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**NOVEL DIPEPTIDYL PEPTIDASE IV INHIBITORS USED FOR
FUNCTIONALLY INFLUENCING DIFFERENT CELLS AND TREATING
IMMUNOLOGICAL, INFLAMMATORY, NEURONAL, AND OTHER DISEASES**

Dipeptidyl peptidase IV (DPIV; CD26; EC 3.4.14.5) is an ubiquitously present serine protease specifically catalyzing the hydrolysis of peptides after proline or alanine in the second position of the N-terminal end. The gene family of DPIV having enzymatic activity also includes, inter alia, DP 8, DP 9 and FAP/seprase (T. Chen et al.: Adv. Exp. Med. Biol. 524, 79, 2003). A substrate specificity similar to DPIV is shown by Attractin (mahagony protein) (J. S. Duke-Cohan et al.: J. Immunol. 156, 1714, 1996). Said enzyme is also inhibited by inhibitors effectively inhibiting DPIV.

For dipeptidyl peptidase IV, attractin and FAP, important biological functions were demonstrated in different cell systems. This is true for the immune system (U. Lendekel et al.: Intern. J. Mol. Med. 4, 17, 1999; T. Kähne et al.: Intern. J. Mol. Med. 4, 3, 1999; I. De Meester et al: Advanc. Exp. Med. Biol. 524, 3, 2002; published International Patent Application WO 01/89569 D1; published International Patent Application No. WO 02/053170 A3; International Patent Application No. PCT/EP 03/07199), the neuronal system (published International Patent Application No. WO 02/053169 A2 and German Patent Application No. 103 37 074.9), the Fibroblasts (German Patent Application No. 103 30 842.3), the Keratinozytes (published International Patent Application No. WO 02/053170 A3), die sebaceous gland cells/Sebocytes (International Patent Application No. PCT/EP 03/02356), for several tumors.

The capability, of DPIV, of specifically inactivating the incretory hormones GIP and GLP has resulted into the development of a new therapeutic concept for treating glucose metabolism disturbances (D. M. Evans: Drugs 5, 577, 2002).

For dipeptidyl peptidase IV and for other peptidases, distinguishable inhibitors are known (Reviews are found in: "D. M. Evans: Drugs 5, 577, 2002").

The isolated inhibition of the dipeptidyl peptidase IV and of analogous peptidases, but particularly the combined inhibition of dipeptidyl peptidase IV and of alanyl aminopeptidases (EC 3.4.11.2 and EC 3.4.11.14) results into a strong inhibition of the DNA synthesis and, thereby, of the cell proliferation in immune cells as well as into a change of the cytokine production, particularly into an induction of the immuno-regulatory effective TGF- β 1 (published International Patent Application No. WO 01/89569 D1 ; published International Patent Application No. WO 02/053170 A3). For regulatory T-cells, alanyl aminopeptidase inhibitors effect a strong induction of TGF- β 1 (International Patent Application No. PCT/EP 03/07199). In the neuronal system, a reduction or deceleration, respectively, of acute and chronic cerebral deterioration processes by an inhibition of dipeptidyl peptidase IV or of analogous enzymes, but particularly by a combined inhibition of DP IV or of analogous enzymes and of alanyl aminopeptidases or of analogous enzymes was demonstrated (published International Patent Application WO 02/053 169 A3 and German laid-open Patent Application No. 103 37 074.9). It could be shown, too, for Fibroblasts (German laid-open Patent Application No. 103 37 074.9), Keratinocytes (published International Patent Application No. WO 02/053 170 A3) and Sebaceous Cells (International Patent Application No. PCT/EP 03/02356) that an inhibition of dipeptidyl peptidase IV, but particularly a combined inhibition of the two enzymes dipeptidyl peptidase IV and of alanyl aminopeptidase effects an inhibition of the growth and a change of the cytokine production.

Thus, there results the surprising fact that the dipeptidyl peptidase IV as well as analogously working enzymes perform fundamental central biological functions in several organs and cell systems, and that an inhibition of this peptidase, but particularly a combined inhibition of this enzyme together with an inhibition of the

alanyl aminopeptidases, represents an effective therapeutic principle for the treatment of different diseases which are chronic in most of the cases.

By using accepted animal models, the Inventors could demonstrate that, particularly, the combined administration of inhibitors of both peptidases effects, in fact, also *in vivo* an inhibition of the growth of different cell systems and a suppression of an excessive immune response, of chronic-inflammatory events as well as of cerebral damage (published International Patent Application WO 01/89569 D1).

The results achieved up to now were, predominantly, obtained by using known inhibitors of dipeptidyl peptidase IV, which are described in the literature and are, in part, commercially available, alone or in combination with inhibitors of the alanyl aminopeptidase, which are known and, in part, commercially available, too.

It was an object of the present invention to find further effective inhibitors of dipeptidyl peptidase IV and of analogous enzymes. In particular, lower molecular and easily accessible compounds were to be found which allow an effective inhibition of dipeptidyl peptidase IV and of analogous enzymes.

Surprisingly, in the course of a high-throughput screening of substance data bases, there were now found novel, predominantly non-peptidic low-molecular inhibitors for the dipeptidyl peptidase IV and for analogous enzymes.

The invention relates to novel substances specifically inhibiting peptidases cleaving Gly-Pro-p-nitroanilide.

Moreover, the invention relates to novel substances which, as such or as starting materials for further substances and in combination with inhibitors of the alanyl aminopeptidases or of analogous enzymes, may be used for a prophylaxis and therapy of diseases connected to an excessive immune response (autoimmune

diseases, allergies and rejections of transplants, sepsis), of other chronic-inflammatory diseases, of neuronal diseases and cerebral damage, diseases of the skin (inter alia acne, psoriasis) and of tumor diseases.

Specifically, the present invention relates to substances of the general formulae D1 to D14 according to claims 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25 and 27 as well as tautomers and stereoisomers of said compounds of the general formulae D1 to D14, as well as pharmaceutically acceptable salts, salt derivatives, tautomers and stereoisomers thereof, for a use in the medical field.

In a specific embodiment, the present invention relates to specific compounds having the specific formulae D1.001 to D14.007 which are covered by the above general formulae D1 to D14, which compounds, as examples and without restricting them to those, are listed in claims 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 and 28 in the form of tables, as well as tautomers and stereoisomers of said compounds of the general formulae D1.001 to D14.007, and pharmaceutically acceptable salts, salt derivatives, tautomers and stereoisomers thereof, for a use in the medical field.

Moreover, the invention relates to pharmaceutical compositions comprising at least one compound having one of the general formulae D1 to D14, optionally in combination with per se known and usual carriers and adjuvants.

Moreover, the invention relates to cosmetic compositions comprising at least one compound having one of the general formulae D1 to D14, optionally in combination with per se known and usual carriers and adjuvants.

Furthermore, the invention relates to the use of at least one compound of one of the general formulae D1 to D14 or of at least one of the above-mentioned pharmaceutical or cosmetic compositions for inhibiting the activity of dipeptidyl peptidase

IV or of analogous enzymes, in a manner alone or in combination with inhibitors of alanyl aminopeptidases or of analogous enzymes.

Furthermore, the invention relates to the use of at least one compound of one of the general formulae D1 to D14 or of at least one of the above-mentioned pharmaceutical or cosmetic compositions for topically influencing the activity of dipeptidyl peptidase IV or of analogous enzymes, in a manner alone or in combination with inhibitors of alanyl aminopeptidases or of analogous enzymes.

Moreover, the invention relates to the use of at least one compound of one of the general formulae D1 to D14 or of at least one of the above-mentioned pharmaceutical or optionally also cosmetic compositions for a prophylaxis and therapy of a number of diseases which, as a matter of an exemplary description, are claimed in claims 33 to 45. In particular embodiments, without that this should be interpreted as restricting the invention, compounds of the general formulae D1 to D14 in accordance with the invention, particularly any of the particularly preferred compounds D1.001 to D14.007 summarized in Tables 1 to 14, may be used as such, or may be used as starting compounds for further compounds or may be used in combination with inhibitors of alanyl aminopeptidases and with inhibitors of analogous enzymes for a therapy of diseases accompanied by an excessive immune response (autoimmune diseases, allergies and transplant rejections), of other chronic-inflammatory diseases, of neuronal diseases and of cerebral damage, diseases of the skin (inter alia acne and psoriasis), tumor diseases and specific virus infections (inter alia SARS).

Furthermore, the invention relates to the use of at least one compound of one of the general formulae D1 to D14 or of at least one of the above-mentioned pharmaceutical or cosmetic compositions for manufacturing a medicament for inhibiting the activity of dipeptidyl peptidase IV or of analogous enzymes, alone or in combination with inhibitors of alanyl aminopeptidases or of analogous enzymes.

Furthermore, the invention relates to the use of at least one compound of one of the general formulae D1 to D14 or of at least one of the above-mentioned pharmaceutical or cosmetic compositions for manufacturing a medicament for topically influencing the activity of dipeptidyl peptidase IV or of analogous enzymes, alone or in combination with inhibitors of alanyl aminopeptidases or of analogous enzymes.

Furthermore, the invention relates to the use of at least one compound of one of the general formulae D1 to D14 or of at least one of the above-mentioned pharmaceutical or optionally also cosmetic compositions for manufacturing a medicament for a prophylactic and therapeutic treatment of a number of diseases claimed, in an exemplifying way, in claims 48 to 60. In particular embodiments, without restricting the invention, the compounds of the general formulae D1 to D14, especially the particularly preferred single compounds D1.001 to D14.007 shown in Tables 1 to 14, may be used, as such or as starting substances for further substances and in combination with inhibitors of alanyl aminopeptidases or of analogous enzymes, for manufacturing a medicament for a therapy of diseases associated with an excessive immune response (autoimmune diseases, allergies or transplant rejections), of other chronic-inflammatory diseases, of neuronal diseases and cerebral damage, of skin diseases (inter alia acne and psoriasis), of tumor diseases and of specific virus infections (inter alia SARS).

Moreover, the invention relates to a process for inhibiting the activity of dipeptidyl peptidase IV and of analogous enzymes, alone or in combination with inhibitors of alanyl aminopeptidases and of analogous enzymes, by an administration of at least one compound of the general formulae D1 to D14 or of at least one of the above pharmaceutical or cosmetic compositions in an amount required for an inhibition of the enzymatic activity.

Moreover, the invention relates to a process for topically influencing the activity of dipeptidyl peptidase IV and of analogous enzymes, alone or in combination with inhibitors of alanyl aminopeptidases and of analogous enzymes, by an administration of at least one compound of the general formulae D1 to D14 or of at least one of the above pharmaceutical or cosmetic compositions in an amount required for influencing the enzymatic activity.

Moreover, the invention relates to a process for a prophylaxis and/or therapy of one of the diseases or conditions claimed in the claims 63 to 76 by inhibiting the activity of dipeptidyl peptidase IV and of analogous enzymes, alone or in combination with inhibitors of alanyl aminopeptidases or of analogous enzymes, by an administration of at least one compound of the general formulae D1 to D14 or of at least one of the above pharmaceutical or cosmetic compositions in an amount required for a prophylactic or therapeutic treatment.

The term "analogous enzymes" as used in the present specification and in the claims relates to enzymes having an enzymatic activity analogous to the one shown by the dipeptidyl peptidase IV. This is applicable, for example, for DP8, DP9, for FAP/seprase or for attractin (DP IV). The above term is also explained, in this sense, in the above-referenced textbook "A. J. Barrett et al.; Handbook of Proteolytic Enzymes, Academic Press, 1998".

In the general formulae D1 to D14, as can be seen from claims 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25 and 27 in a general form, the residues Rn, i. e. the residues R1, R2, R3, R4, R5, R6, R7, R8, R9 and R10, independent of each other represent a residue selected from the group consisting of hydrogen, unsubstituted or substituted, straight chain or branched C₁ - to C₁₂ alkyl, C₂- to C₁₂ alkenyl and C₂- to C₁₂ alkynyl, hydroxy, thiol, C₁ - to C₁₂ alkoxy, C₁ - to C₁₂ alkylthio, unsubstituted or substituted, uncondensed or condensed, aryl and cycloalkyl optionally containing one or several hetero atoms from the group of N, O, P and S, unsubstituted or substi-

tuted amino, unsubstituted or substituted carbonyl, unsubstituted or substituted thiocarbonyl and unsubstituted or substituted imino.

In detail, the residues R_n, in embodiments of the invention where they represent unsubstituted straight chain or branched alkyl groups having 1 to 12 carbon atoms, represent in preferred embodiments methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, tert-butyl, n-pentyl, i-pentyl, sec-pentyl, tert-pentyl, n-hexyl, i-hexyl, 3-methylpentyl, 2-ethylbutyl, 2,2-dimethylbutyl as well as all straight chain and branched isomers for the residues heptyl, octyl, nonyl, decyl, undecyl and dodecyl. In accordance with the invention, particularly preferred from the above-mentioned group are alkyl groups having 1 to 6 carbon atoms; among those, the residues methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and tert-butyl are even more preferred.

In other embodiments according to the invention, the residues R_n, in cases where they represent unsubstituted straight chain or branched alkenyl groups having 2 to 12 carbon atoms, represent in preferred embodiments vinyl, allyl, 1-butenyl, 2-butenyl and all straight chain and branched residues for the radicals pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, undecenyl and dodecenyl, also with respect to the position of the C=C double bond. In further embodiments of the invention, the residues R_n may also represent straight chain or branched alkenyl groups having several double bonds. Preferred residues of this group are the butadienyl group and the isoprenyl group. Among the above-mentioned groups, particularly preferred in accordance with the invention are the alkenyl groups having 2 to 6 carbon atoms; of those, the vinyl, allyl, 1-butenyl and 2-butenyl groups are even more preferred.

In other embodiments according to the invention, the residues R_n, in cases where they represent unsubstituted straight chain or branched alkynyl groups having 2 to 12 carbon atoms, represent in preferred embodiments ethynyl, propynyl, 1-butynyl,

2-butynyl and all straight chain and branched residues for the radicals pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, undecynyl and dodecynyl, also with respect to the position of the C≡C triple bond. Among the above-mentioned groups, particularly preferred in accordance with the invention are the alkynyl groups having 2 to 6 carbon atoms; of those, the groups ethynyl, propynyl, 1-butynyl and 2-butynyl are even more preferred.

In accordance with the invention, straight chain and branched alkyl, alkenyl and alkynyl residues may be substituted in a further embodiment of the invention. The substituent(s) may be positioned at any desired position of the backbone made of carbon atoms and may be selected from the group consisting of halogen atoms as fluorine, chlorine, bromine and iodine, alkyl groups having 1 to 6 carbon atoms, alkoxy groups having 1 to 6 carbon atoms in the alkyl residue and amino groups which may be unsubstituted or substituted with one or two alkyl residues independently of each other and having 1 to 6 carbon atoms.

In further embodiments of the invention, the residues R_n in the general formulae D₁ to D₁₄ represent C₁ - to C₁₂ alkoxy residues or C₁ - to C₁₂ alkylthio residues. Also for the C₁ - to C₁₂ alkyl residues of these alkoxy and alkylthio groups, the above definitions of the straight chain and branched alkyl residues are applicable. Particularly preferred are straight chain C₁ - to C₆ alkoxy groups and straight chain C₁ - to C₆ alkylthio groups, and particularly preferred are the residues methoxy, ethoxy, n-propoxy, methylthio, ethylthio and n-propylthio.

In further embodiments of the invention, the residues R_n in the general formulae D₁ to D₁₄ may also represent unsubstituted or substituted cycloalkyl residues. In accordance with the invention, the cycloalkyl residues may preferably contain three to eight atoms in the ring and may consist exclusively of carbon atoms or may contain one or several hetero atom(s). Among the purely carbocyclic rings, the residues cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclo-

hexadienyl, cycloheptyl, cycloheptenyl, cycloheptadienyl and cycloheptatrienyl are particularly preferred. Examples for hetero atom-containing cycloalkyl residues are, in further embodiments of the invention, the residues tetrahydrofuranyl, pyrrolidinyl, imidazolinidyl, piperidinyl, piperazinyl and morpholinyl. Substituents to these carbocyclic and heterocyclic cycloalkyl residues may be selected from the above group of substituents of linear alkyl groups.

In further embodiments of the invention, the residues Rn in the compounds of the general formulae D1 to D14 may represent uncondensed or condensed aryl residues optionally containing one or several hetero atoms from the group of N, O, P and S. The aryl residues may have one ring or may have several rings and, if having several rings, two rings are preferred. Moreover, one ring may preferably have five, six or seven ring members. In systems consisting of several rings condensed to each other, benzo-condensed rings are particularly preferred, i. e. ring systems wherein at least one of the rings is an aromatic six-membered ring. Particularly preferred are aryl residues purely consisting of carbon atoms, selected from phenyl, cyclopentadienyl, cycloheptatrienyl and naphthyl. Particularly preferred aryl residues containing hetero atoms are, for example, selected from the group consisting of indolyl, cumaronyl, thionaphthenyl, quinolinyl (benzopyridyl), quinazolinyl (benzopyrimidinyl) and quinoxylinyl (benzopyrazinyl).

In another embodiment of the invention, cyclic residues either consisting of one ring or consisting of several rings, either containing carbon atoms exclusively or also containing hetero atoms, either aromatic systems or non-aromatic systems, may be substituted. The substituents may be bound to any position of the ring system, either to a carbon atom or to a hetero atom. They may be selected from the group consisting of halogen atoms as, for example, fluorine, chlorine, bromine and iodine, alkyl groups having 1 to 6 carbon atoms, alkoxy groups having 1 to 6 carbon atoms in the alkyl group, and unsubstituted amino groups or amino groups

substituted with one or two alkyl groups having – independent of each other - 1 to 6 alkyl groups.

Moreover, in accordance with the invention, the residues Rn (= R1 to R10) may also represent unsubstituted amino residues (-NH₂) or unsubstituted imino residues (-NH-) or substituted amino residues (-NHR₁ or -NR₁R_m) or substituted imino residues (-NR_m-). Herein, the residues R₁ and R_m may have the meanings defined above in detail for the residues Rn, and they may be identical or different.

In accordance with the invention, the residues Rn (= R1 to R10) may also represent unsubstituted carbonyl residues (H-(C=O)-) or unsubstituted thiocarbonyl residues (H-(C=S)-) or for substituted carbonyl residues (R_m-(C=O)-) or substituted thiocarbonyl residues (R_m-(C=S)-). In these residues, the substituents R_m of substituted carbonyl residues or substituted thiocarbonyl residues have the meanings defined above for the possible substituents of the residues Rn.

In accordance with the invention, the above-mentioned residues Rn (= R1, R2, R3, R4, R5, R6, R7, R8, R9 and/or R10) may be bound to the respective basic structures of the general formulae D1 to D14 via one of their carbon atoms. In an alternative embodiment, it is also possible that the residues Rn are bound to the respective basic structures of the general formulae D1 to D14 via the hetero atom or via one of their hetero atoms.

In several of the general formulae D1 to D14 (for example in the general formulae D1(b), D2, D7(a) to (c), D8, D9(a) to (c), D12, D13 and D14), Y, Y₁ and Y₂ represent residues bound to the basic structure of the respective formula via a C=Y double bond (or a C=Y₁ double bond and/or a C=Y₂ double bond). In the formulae where they appear, the groups Y represent – independent of each other – one of the residues O, S or NR_n, for example NR₃, NR₄ or NR₅, bound to a carbon atom via a double bond. In the latter residues, the radicals Rn (for example R₃, R₄, R₅)

may have the meanings mentioned above, including the meaning "hydrogen". Particularly preferably, Y represents O bound to a carbon atom via a double bond.

In several of the general formulae D1 to D14 (for example in the formulae D3, D5, D6), X, X₁, X₂ and Z represent residues bound to two different carbon atoms via a C-X single bond each (or via a C-X₁ single bond or via a C-X₂ single bond) or via a C-Z single bond each. In the general formulae where they appear, the residues X and Z represent – independent of each other – the residues >NH, >NR_n (for example >NR₅ or >NR₁₀), -O-, -S- -CH₂- , -CHR_n- or -CR_n2-, bound to two different carbon atoms by a single bond each, wherein the residues R_n have the meaning given above, or they represent the residues >N-, >CH- or >CR_n- (for example >CR₈- or >CR₉-) bound to three different carbon atoms via a single bond each, wherein R_n (for example R₈, R₉) have the meanings given above.

In the compounds of the general formula D4, R₁₁ and R₁₂ represent heterocyclic systems having three to eight ring members which are bound to each other directly via hetero atoms, via carbon atoms or via hetero atoms and carbon atoms. The partial rings designated as R₁ and R₂ may be substituted or unsubstituted, condensed or non-condensed and may contain zero to three double bonds and may contain further hetero atoms and hetero atom-containing groups.

In the compounds of the general formula D9, Z represents P or S.

In the compounds having the general formulae D8, D12, D13, X and Z independent of each other represent residues from the group consisting of hydroxy, thiol, C₁ - to C₁₂ alkoxy, C₁ - to C₁₂ alkylthio, unsubstituted or substituted, uncondensed or condensed aryl or cycloalkyl optionally containing one or several hetero atoms from the group of N, O, P and S, and amino (NH₂, NHR₁, NR₁R₂), wherein all above-mentioned meanings of X and Z correspond to the meanings for alkoxy, alkylthio,

aryl, cycloalkyl and amino which were defined above in detail for the residues Rn of the general formulae D1 to D14.

The compounds of the general formulae D1 to D14 (in general) as defined in claims 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25 and 27 and the compounds D1.001 to D14.007 in Tables 1 to 14 in the claims 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 and 28 (specifically) may be prepared in accordance with processes known from the literature or are commercially available.

The compounds corresponding to the general formulae D1 to D14 (in general) and the specific compounds D1.001 to D14.007 indicated in Tables 1 to 14 (in preferred embodiments of the invention) are claimed for a use in the medical field. The term "for a use in the medical field" is understood here, and in the claims as well, in its broadest sense and relates to all conceivable fields of application, where the compounds of the general formulae D1 to D14 defined by the present invention, and the compounds D1.001 to D14.007 as mentioned in Tables 1 to 14, in preferred embodiments, may exert an effect in connection to medically relevant conditions of the body of a mammal, in particular of the body of a human.

In connection to such medically relevant conditions, the compounds of the general formulae D1 to D14 (in general) and the preferred compounds D1.001 to D14.007 according to Tables 1 to 14 are used either in the form of a single compound or are used in the form of more than one compound, or several compounds, of the general formulae D1 to D14 (in particular of the compounds D1.001 to D14.007 according to Tables 1 to 14). Also covered by the scope of the present invention is a use of one or more than one compound of the general formulae D1 to D14, preferably of one or more than one compound selected from the group consisting of the compounds D1.001 to D14.007 according to Tables 1 to 14, in combination with other effective agents, for example one or more than one compound having an effect in the inhibition of dipeptidyl peptidase IV or of analogous enzymes (i. e. of

enzymes having an equal substrate specificity) and/or having an effect in the inhibition of alanyl aminopeptidases (APN) or of analogous enzymes (i. e. of enzymes having an equal substrate specificity). Examples of such compounds having an effect as enzyme inhibitor(s) are mentioned in parallel patent applications filed by the Applicants of the present application on the same filing date as the present application as well as in the Applicants' patent applications referred to in the introduction to the present description, the whole disclosed content of which applications is incorporated into the present specification by this reference.

Specific examples of inhibitors effective as inhibitors of dipeptidyl peptidase IV or of analogous enzymes, which are known from the prior art and may optionally be used together with the compounds of the present invention particularly with one or several of the compounds D1.001 to D14.007 according to Tables 1 to 14, include, for example: Xaa-Pro dipeptides, corresponding derivatives, preferably dipeptide phosphonic acid diaryl esters, dipeptide boronic acids (e. g. Pro-bobo-Pro) and their salts, Xaa-Xaa-(Trp)-Pro-(Xaa)_n peptides ($n = 0$ to 10), corresponding derivatives and their salts, and amino acid (Xaa) amides, corresponding derivatives and their salts, wherein Xaa is an α -amino acid/imino acid or an α -amino acid derivative/imino acid derivative, preferably N^c-4-nitrobenzyl-oxycarbonyl-L-lysine, L-proline, L-tryptophane, L-isoleucine, L-valine, and cyclic amines as, for example pyrrolidine, piperidine, thiazolidine and their derivatives act as the amide structure. Such compounds and their preparation were described in an earlier patent (K. Neubert et al.; DD 29 60 75 A5). Furthermore, tryptophane-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives (TSL) and (2S,2S',2S'')-2-[2''-amino-3''-(indol-3'''-yl)-1''-oxopropyl]-1',2',3',4'-tetrahydro-6'8'-dihydroxy-7-methoxyisoquinol-3-yl-carbonyl-amino]-4-hydrome-thyl-5-hydropentanoic acid (TMC-2A) may advantageously be used as the effectors for the DP IV together with the compounds of the general formulae D1 to D14. One example of an inhibitor of DP IV preferably useable together with the compounds of the general formulae D1

to D14 is Lys[Z(NO₂)] thiazolidide, wherein Lys represents an L-lysine residue and Z(NO₂) represents 4-nitrobenzyl-oxycarbonyl (see also DD 29 60 75 A5).

Specific examples of inhibitors effective as inhibitors of alanyl aminopeptidase, which are known from the prior art and may optionally be used together with the compounds of the present invention particularly with one or several of the compounds D1.001 to D14.007 according to Tables 1 to 14, include, for example: actinonine, leuhistidine, phebestine, amastatine, bestatine, probestine, β -amino thiols, α -amino phosphinic acids, α -amino phosphinic acid derivatives, preferably D-Phe- ψ -[PO(OH)-CH₂]-Phe-Phe. Known alanyl aminopeptidase inhibitors particularly preferred and useable together with the compounds of the present invention are bestatine (Ubenimex), actinonine, probestine, phebestine, RB3014 or leuhistidine.

Another embodiment of the present invention relates to pharmaceutical compositions, which comprise at least one, optionally two or even more, compound(s) of the general formulae D1 to D14, particularly preferably selected from the compounds D1.001 to D14.007 according to Tables 1 to 14. Such pharmaceutical compositions comprise one or several of said compounds in such amounts required for exerting a pharmaceutical effect. Such amounts may in detail be determined by a skilled person by a few routine tests and without adding an inventive activity. In general, these amounts are in ranges of from 0.01 to 1000 mg of each of the compounds of the general formulae D1 to D14, particularly preferred of the compounds D1.001 to D14.007 according to Tables 1 to 14, per administration unit, even more preferred in ranges of from 0.1 to 100 mg of each of said compounds per administration unit. Moreover, amounts adjusted to the respective single mammalian organism or human organism may easily be determined by a skilled person, and it may also be provided that a sufficient concentration of the compound(s) to be used may be achieved by an administration of divided or of several administration units.

Another embodiment of the present invention relates to cosmetic compositions, which comprise at least one, optionally two or even more, compound(s) of the general formulae D1 to D14, particularly preferably selected from the compounds D1.001 to D14.007 according to Tables 1 to 14. Such cosmetic compositions comprise one or several of said compounds in such amounts required for exerting a desired effect, for example a cosmetic effect. Such amounts may in detail be determined by a skilled person by a few routine tests and without adding an inventive activity. In general, these amounts are in ranges of from 0.01 to 1000 mg of each of the compounds of the general formulae D1 to D14, particularly preferred of the compounds D1.001 to D14.007 according to Tables 1 to 14, per administration unit, even more preferred in ranges of from 0.1 to 100 mg of each of said compounds per administration unit. Moreover, amounts adjusted to the respective single mammalian organism or human organism may easily be determined by a skilled person, and it may also be provided that a sufficient concentration of the compound(s) to be used may be achieved by an administration of divided or of several administration units.

The one compound or the several compounds according to the present invention or pharmaceutical or cosmetic compositions containing it/them is/are administered simultaneously with known carrier substances and/or auxiliary substances (adjuvants). Such carrier and auxiliary substances are known to a skilled person as such and also with respect to their function and way of application and need no detailed explanation here.

The invention also comprises pharmaceutical compositions which comprise: one or several of the inhibitors of the DP IV or of the inhibitors of enzymes having a DP IV-analogous enzymatic activity and/or of the inhibitors of the APN or of the inhibitors of enzymes having an APN-analogous enzymatic activity in accordance with the prior art, together with one or with several compound(s) of the general formulae D1 to D14, particularly preferably together with one or several

compound(s) which are selected from the compounds D1.001 to D14.007 of the Tables 1 to 14, in a spaced apart formulation in combination with known carrier substances, auxiliary substances and/or additives for a simultaneous or, with respect to the time, immediately successive administration with the aim of a joint effect.

The administration of the compounds of the general formulae D1 to D14 in general and, preferably, of the compounds D1.001 to D14.007 according to Tables 1 to 14 or the administration of pharmaceutical or cosmetic compositions comprising one or several of the above compounds together with usual carrier substances, auxiliary substances and/or additives, is effected, on the one hand, as a topical application in the form of, for example, creams, ointments, pastes, gels, solutions, sprays, liposomes and nanosomes, lotion, "pegylated" formulations, degradable (i.e. decomposable under physiological conditions) depot matrices, hydrocolloid dressings, plasters, micro-sponges, prepolymers and similar novel carrier substrates, jet injections and other dermatological bases/vehicles including instillative application, and on the other hand, as a systemic application for an oral, transdermal, intravenous, subcutaneous, intracutaneous, intramuscular or intrathecal application in suitable recipes or in suitable galenic forms.

In accordance with the invention, the compounds of the general formulae D1 to D14 in general, and preferably the compounds D1.001 to D14.007 according to Tables 1 to 14, alone or in combination, or pharmaceutical or cosmetic compositions comprising one or several of said compounds are used for an inhibition of the activity of the dipeptidyl peptidase IV or of analogous enzymes, alone or in combination with other inhibitors of the alanyl aminopeptidases or of analogous enzymes.

In another embodiment, the compounds of the general formulae D1 to D14 in general, and preferably the compounds D1.001 to D14.007 according to Tables 1

to 14, alone or in combination, or pharmaceutical or cosmetic compositions comprising one or several of said compounds are used for topically influencing the activity of the dipeptidyl peptidase IV or of analogous enzymes, alone or in combination with other inhibitors of the alanyl aminopeptidases or of analogous enzymes.

In preferred embodiments of the invention, the compounds of the general formulae D1 to D14 in general, and preferably the compounds D1.001 to D14.007 according to Tables 1 to 14, alone or in combination, or pharmaceutical or cosmetic compositions comprising one or several of said compounds are used for a prophylaxis and a therapy of diseases as, for example: multiple sclerosis, Morbus Crohn, Colitis ulcerosa and of other autoimmune diseases as well as of inflammatory diseases, of Asthma bronchiale and of other allergic diseases, of skin and mucosa diseases, for example psoriasis, acne, and of dermatologic diseases being accompanied by a hyperproliferation and by changed differentiation states of fibroblasts, of benign fibrosing and sclerosing skin diseases and of malign fibroblastar hyperproliferation states, of acute neuronal diseases as, for example, ischemia-caused cerebral damage after an ischemic or hemorrhagic stroke, craniocerebral trauma, heart arrest, myocardial infarct or as a consequence of heart surgery, of chronic neuronal diseases, for example Morbus Alzheimer, Pick's disease, of the progressive supranuclear palsy, of a corticobasal degeneration, of a frontotemporal dementia, of Morbus Parkinson, particularly of Morbus Parkinson coupled to the chromosome 17, of Morbus Huntington, of disease states caused by prions, and of amyotrophic lateral sclerosis, of arteriosclerosis, of arterial inflammations, of a stent restenosis, of chronic obstructive pulmonary diseases (Chronisch Obstruktive Lungenerkrankungen; COPD), of tumors, of metastases, of prostate tumors, of the Heavy Acute Respiratory Syndrome (SARS) and of sepsis and sepsis-like conditions.

In a further preferred embodiment of the invention, the compounds of the general formulae D1 to D14 in general, and preferably the compounds D1.001 to D14.007 according to Tables 1 to 14, alone or in combination, or pharmaceutical or cosmetic compositions comprising one or several of said compounds are used for a prophylaxis and a therapy of a rejection of transplanted tissues and cells. As an example of such an application, there may be mentioned the use of one or of several of the above-mentioned compounds or of a pharmaceutical composition containing one or several of the said compounds in connection with allogenic kidney transplants or stem cell trans-plants.

In a further preferred embodiment of the invention, the compounds of the general formulae D1 to D14 in general, and preferably the compounds D1.001 to D14.007 according to Tables 1 to 14, alone or in combination, or pharmaceutical or cosmetic compositions comprising one or several of said compounds are used for a prophylaxis and a therapy of rejection and inflammation reactions at, or by, medical devices implanted into an organism ("medical devices"). These may comprise, for example, stents, articulation implants (knee joint implants, hip joint implants), bone implants, heart pacemakers, or other implants. In a further preferred embodiment of the invention, the compounds of the general formulae D1 to D14 in general, and preferably the compounds D1.001 to D14.007 according to Tables 1 to 14, alone or in combination, or pharmaceutical or cosmetic compositions comprising one or several of said compounds are used in such a way that the compound(s) or composition(s) is/are applied onto the article or articles in the form of a coating or layer, or at least one of the compounds or compositions is admixed, as a substance, to the material of the article or articles. Also in this case, it is possible – of course – that at least one of the compounds or compositions is administered locally or systemically, optionally successively or parallel in time.

In a similar way as described above, and for similar purposes or for the prophylaxis and therapy of the above diseases and conditions mentioned as examples,

however without any restriction, the compounds of the general formulae D1 to D14 in general, and preferably the compounds D1.001 to D14.007 according to Tables 1 to 14, alone or in combination, or the above-mentioned pharmaceutical or cosmetic compositions comprising one or several of said above-mentioned compounds may be used for the preparation of a medicament for a prophylaxis and a therapy of the above-mentioned diseases or conditions. These medicaments may comprise said compounds in the amounts specified above, optionally together with known carrier substances, auxiliary substances and/or additives.

Finally, the invention also relates to a process for inhibiting the activity of dipeptidyl peptidase IV and of analogous enzymes, alone or in combination with inhibitors of the alanyl aminopeptidases or of analogous enzymes by an administration of at least one compound or pharmaceutical or cosmetic composition according to the above detailed description in an amount required for an inhibition of the enzyme activity. The amounts of one of the compounds of the general formulae D1 to D14 in general and of the compounds D1.001 to D14.013 according to Tables 1 to 14 are – as indicated above – in the range of from 0.01 to 1000 mg of one compound per administration unit, preferably in the range of from 0.1 to 100 mg of one compound per administration unit.

The invention also relates to a process for topically influencing the activity of dipeptidyl peptidase IV and of analogous enzymes, alone or in combination with inhibitors of the alanyl aminopeptidases or of analogous enzymes by an administration of at least one compound or pharmaceutical or cosmetic composition according to the above detailed description in an amount required for topically influencing the enzyme activity. Also in these cases, the amounts of said compound(s) are in the above-indicated range.

Furthermore, the invention also relates to a process for the prophylaxis and therapy of a plurality of diseases, for example diseases accompanied by an

excessive immune response (autoimmune diseases, allergies, transplant rejections), of other chronically inflammatory diseases, of neuronal diseases and cerebral damage, of skin diseases (*inter alia* acne and psoriasis), of tumor diseases and of specific virus diseases (*inter alia* SARS), and particularly of the diseases mentioned above in detail, by an administration of at least one compound or of a pharmaceutical or cosmetic composition in accordance with the above detailed description in an amount required for the prophylaxis and therapy of the respective disease. Also in these cases, the amounts of the above compound(s) are in the above-mentioned range of from 0.01 to 1000 mg of one compound per administration unit, preferably in the range of from 0.1 to 100 mg of one compound per administration unit.

In the following, the invention is in more detail explained by specific preferred exemplary embodiments. Those exemplary embodiments, however, do not serve a limitation of the invention, but only an exemplifying explanation.

Examples

Example 1:

Inhibition characteristics of the novel inhibitors of the dipeptidyl peptidase IV

In the following Tables (Tables 1 to 14), novel inhibitors are summarized, for which the inventors could show that these substances are capable of inhibiting dipeptidyl peptidase IV and enzymes having an analog effect in their enzymatic activity. The inhibition characteristics measured are referred to as IC-50 values or ID50 values (the latter marked with "") for said enzyme. The enzymatic activity was determined by means of the fluorogenic substrate (Ala-Pro)₂-rhodamine 110.

Table 1:

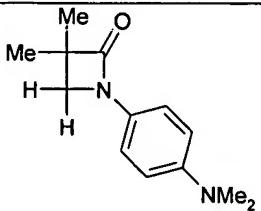
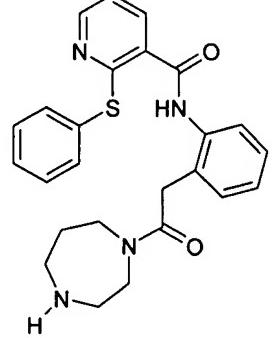
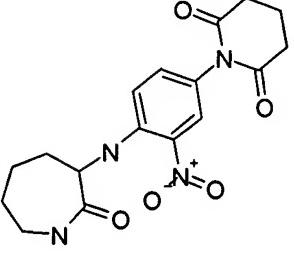
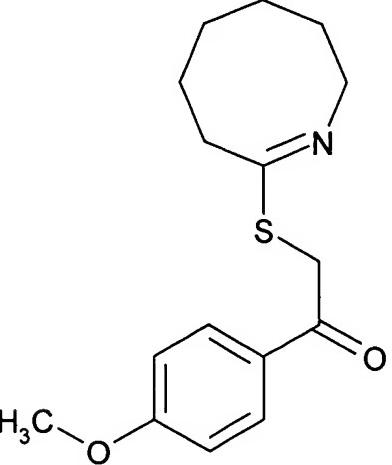
Compound ID.	Structure	IC50_{DPIV} [μM]
D1.001		1.2*
D1.002		1.4*
D1.003		34.14
D1.004		36.51

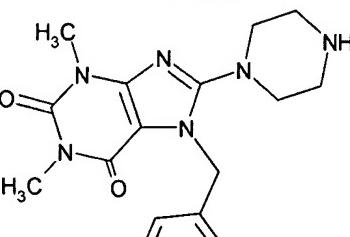
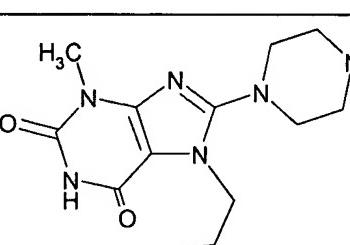
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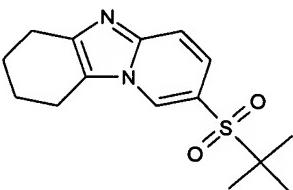
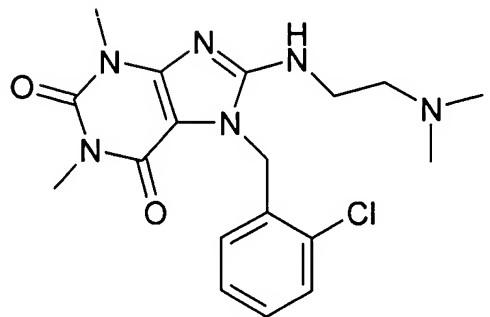
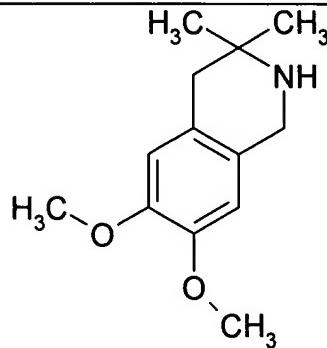
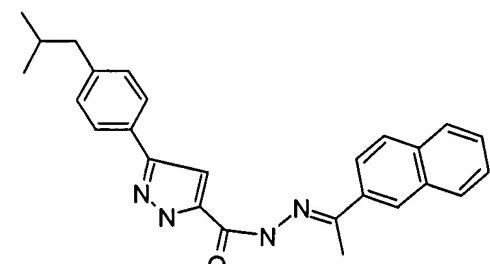
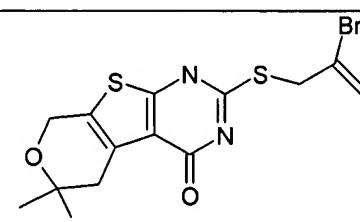
Compound ID.	Structure	IC50 _{DPIV} [μM]
D2.001		14.0
D2.003		32.8
D2.004		33.4
D2.005		54.5
D2.006		132.7*

P29678.S01

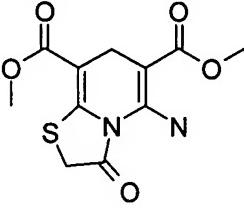
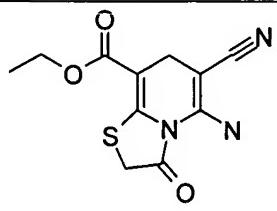
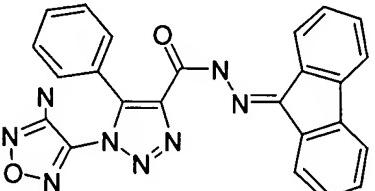
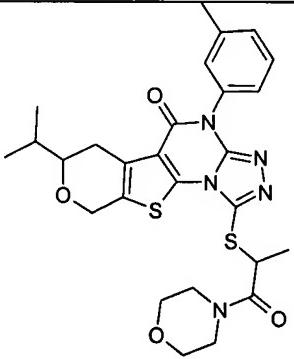
D2.007		148.4*
D2.008		275.4*

Table 3:

Compound ID.	Structure	IC50 _{DPIV} [μM]
D3.001		0.4*
D3.002		0.8*

D3.003		15.6
D3.004		7.5
D3.005		6.0
D3.006		7.2*
D3.007		7.4

P29678.S01

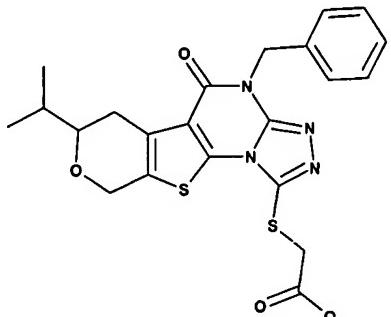
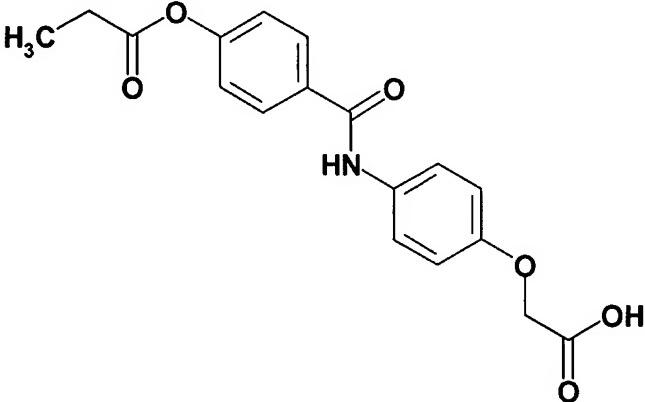
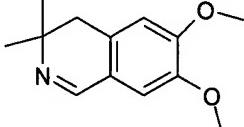
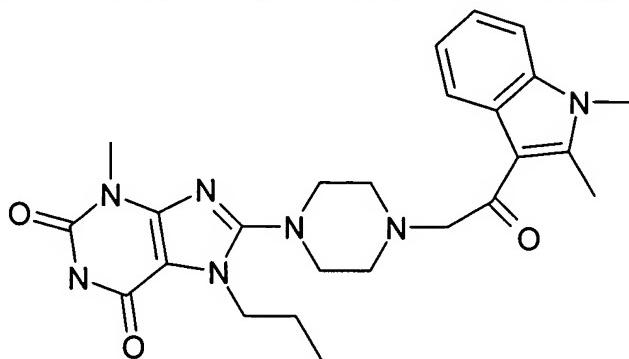
D3.008		34.1
D3.009		14.1
D3.010		8.1
D3.011		10.1
D3.012		10.1

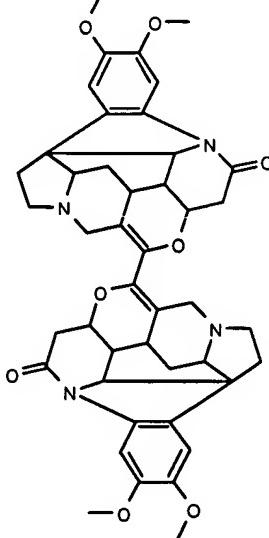
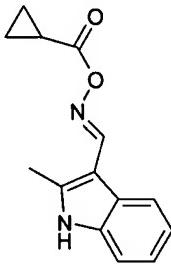
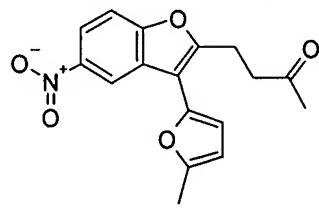
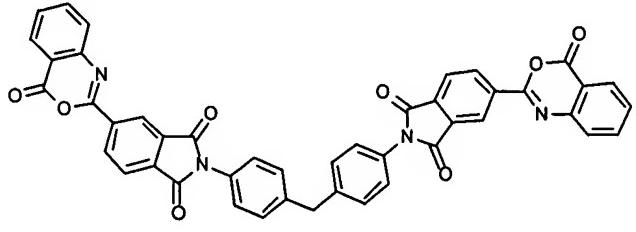
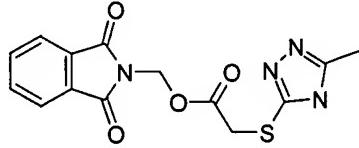
D3.013		10.8
D3.014		12.1
D3.015		12.2
D3.016		12.4
D3.017		14.0
D3.018		14.4

P29678.S01

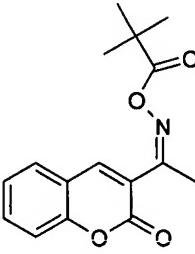
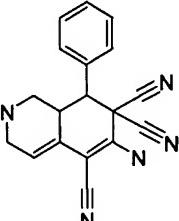
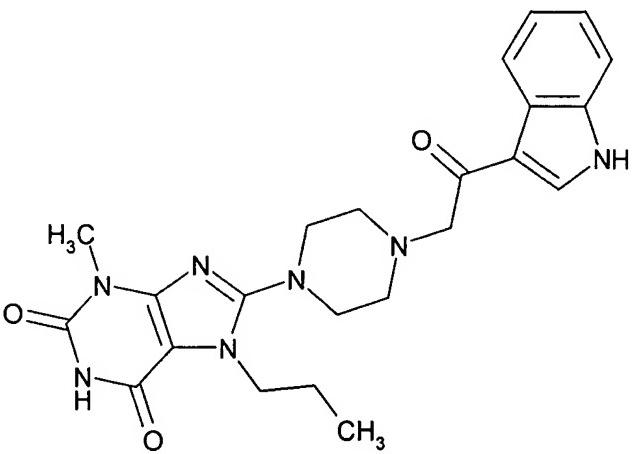
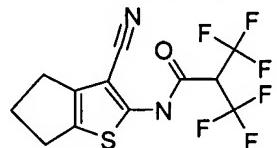
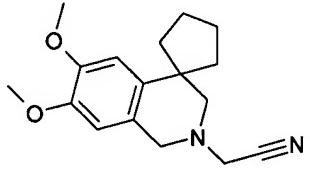
D3.019		14.5
D3.020		15.2
D3.021		15.2
D3.022		16.2
D3.023		18.2

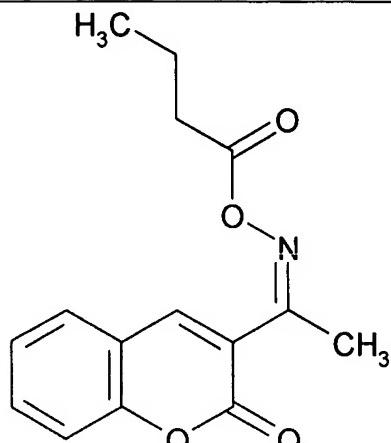
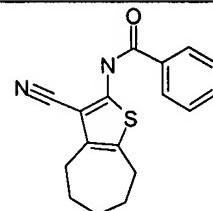
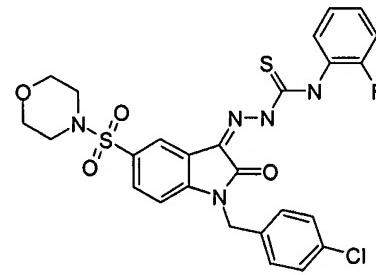
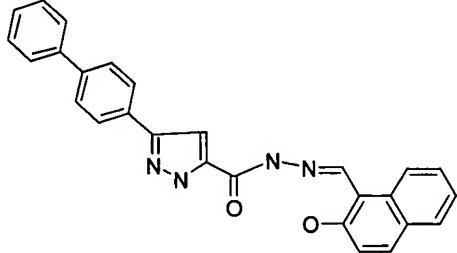
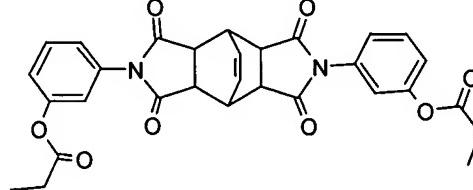
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D3.025		23.8
D3.026		20.2
D3.027		15.2

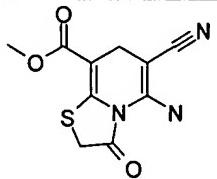
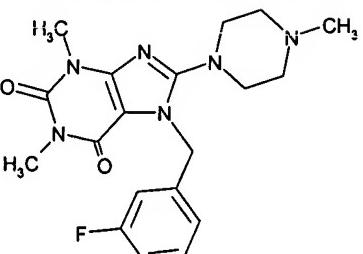
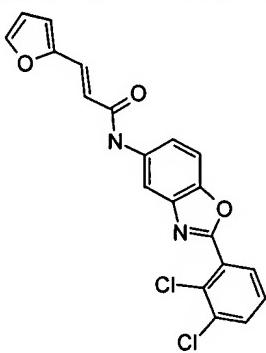
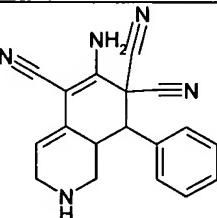
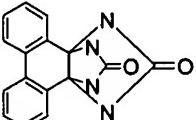
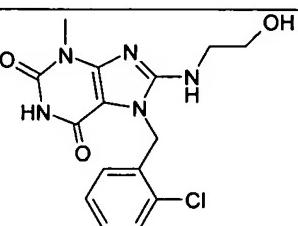
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D3.031		25.4
D3.032		27.2
D3.033		27.5

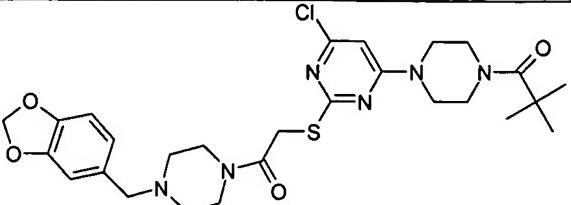
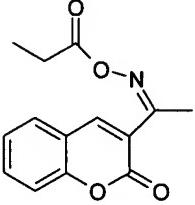
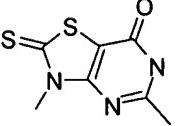
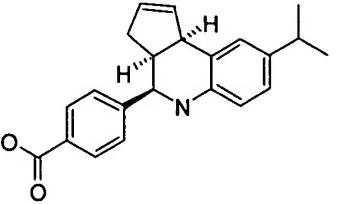
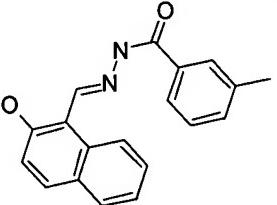
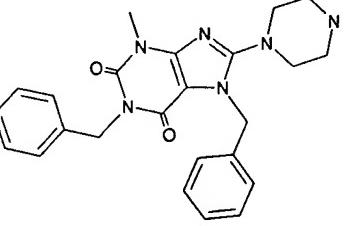
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D3.037		30.8
D3.038		30.9
D3.039		31.4

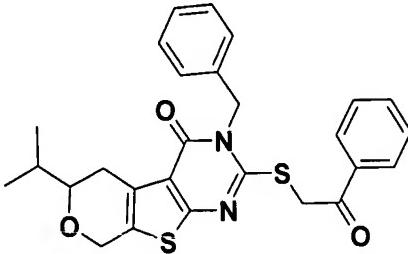
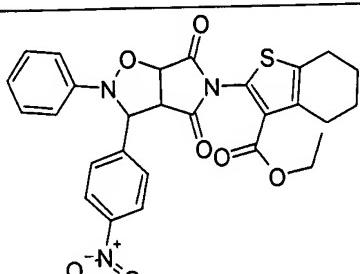
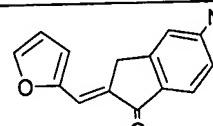
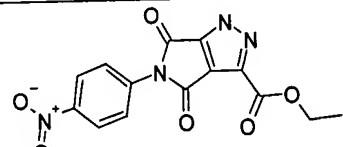
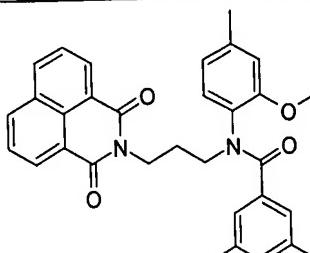
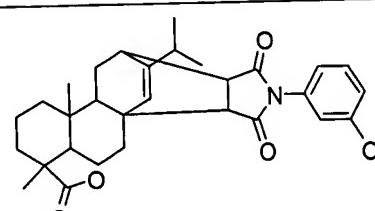
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D3.043		33.4
D3.044		33.5
D3.045		4.2*

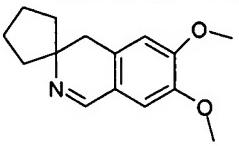
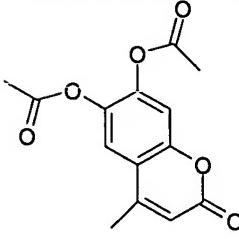
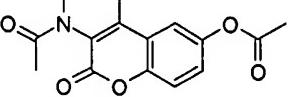
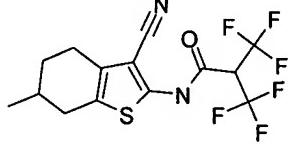
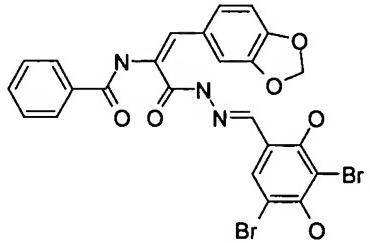
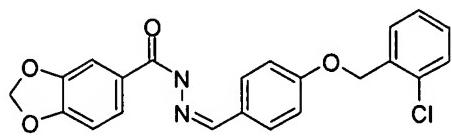
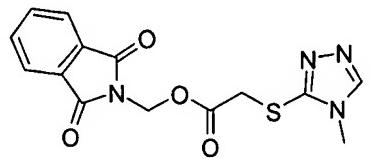
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D3.050		39.8
D3.051		40.2

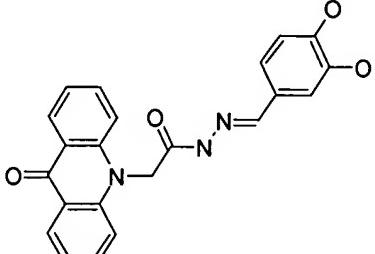
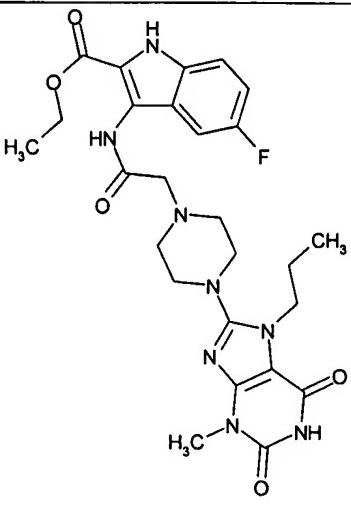
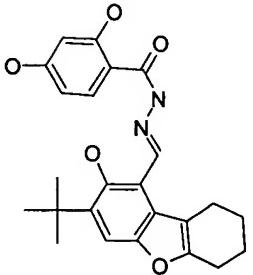
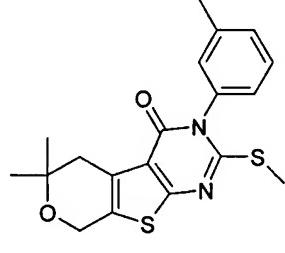
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D3.058		44.0

D3.059		45.6
D3.060		45.9
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D3.066		52.3

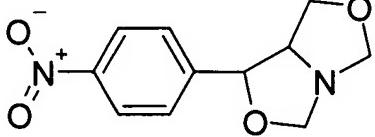
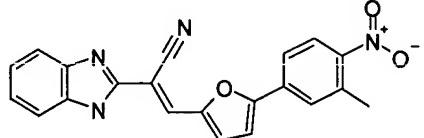
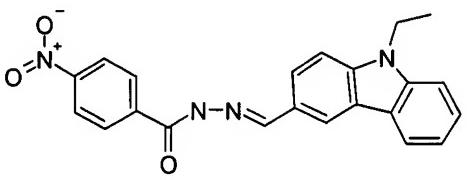
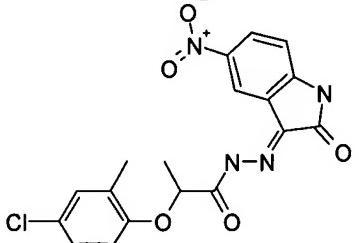
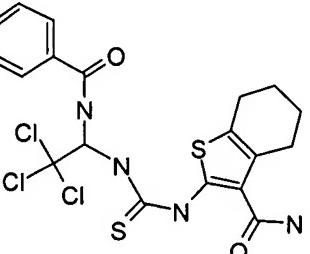
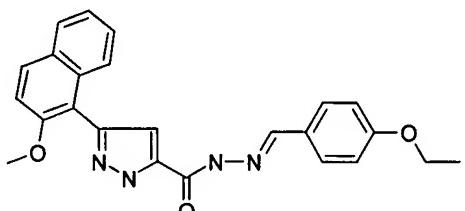
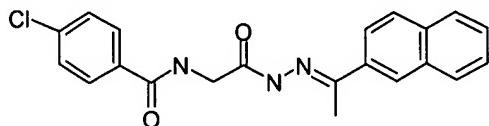
P29678.S01

D3.067		52.4
D3.069		54.1
D3.070		27.5
D3.072		54.5
D3.073		55.4
D3.074		55.4

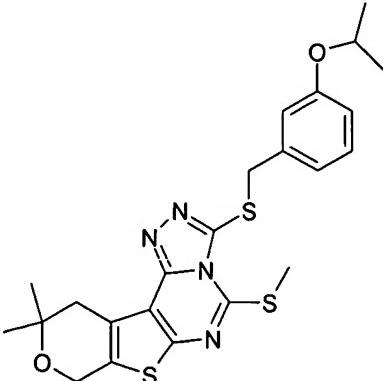
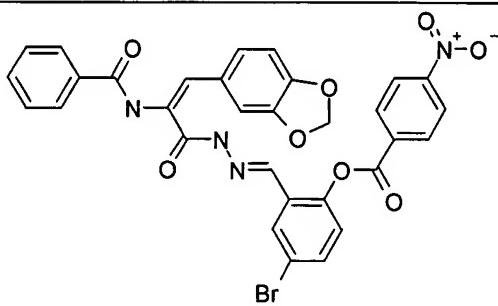
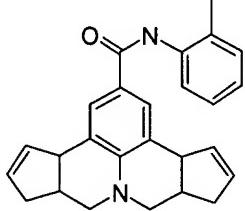
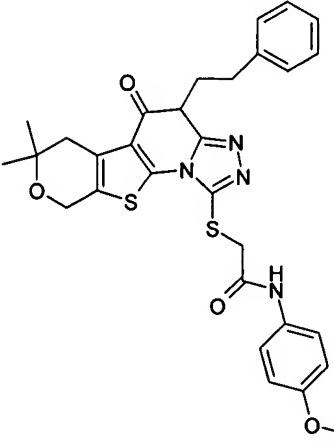
D3.077		59.1
D3.078		59.2
D3.079		59.4
D3.080		59.8
D3.081		60.0
D3.082		62.1
D3.083		62.4

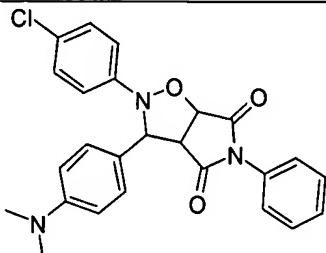
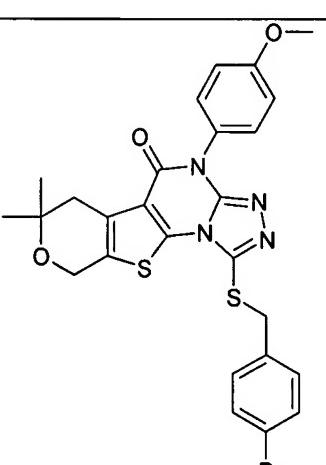
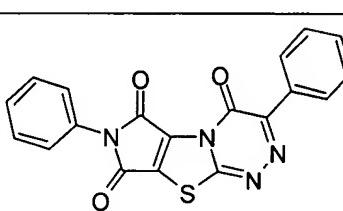
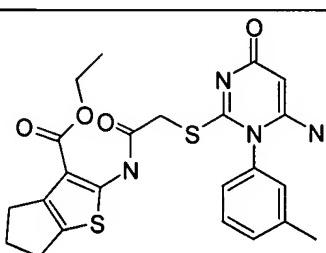
D3.084		63.5*
D3.086		69.8*
D3.087		74.7*
D3.088		80.6

P29678.S01

D3.095		42.4
D3.096		138.3
D3.097		165.3*
D3.098		165.9*
D3.099		168.9*
D3.100		56.3
D3.101		208.3*

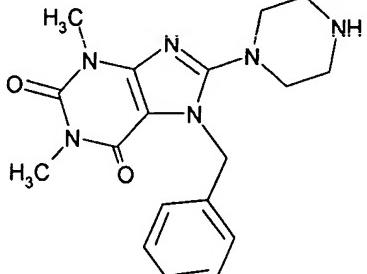
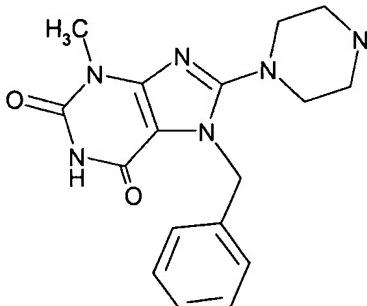
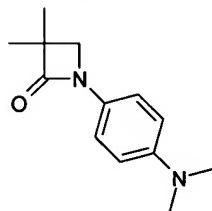
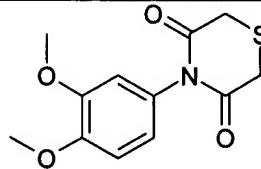
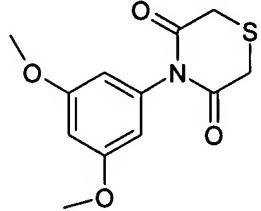
D3.102		208.9*
D3.103		224.1*
D3.104		28.8
D3.105		251.7*
D3.106		255.3*
D3.107		267.9*

D3.108		269.0*
D3.109		271.8*
D3.110		279.4*
D3.111		283.9*

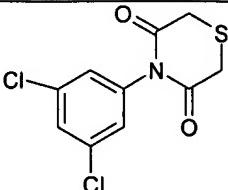
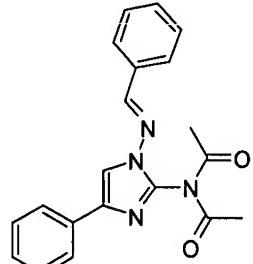
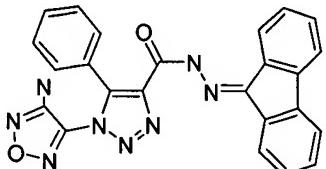
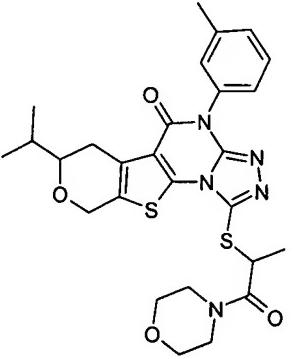
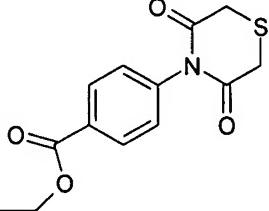
D3.112		343.7*
D3.113		316.8*
D3.114		332.3*
D3.116		362.6*

D3.117		401.9*
D3.118		416.9*
D3.119		527.4*
D3.120		655.7*

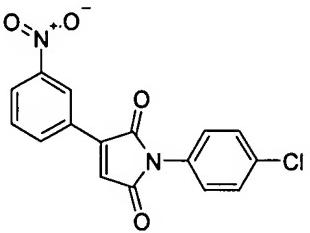
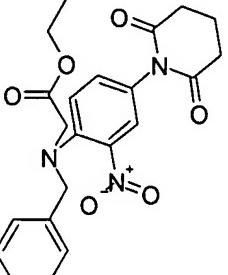
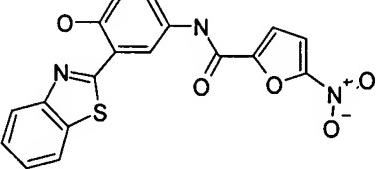
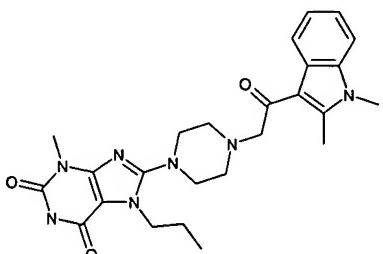
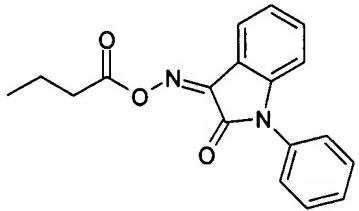
Table 4:

Compound ID.	Structure	IC50_{DPIV} [μM]
D4.001		0.4*
D4.002		0.8*
D4.003		1.2*
D4.004		3.1*
D4.005		3.8*

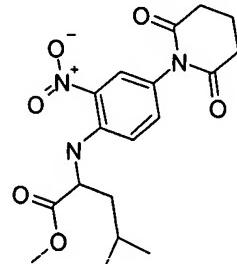
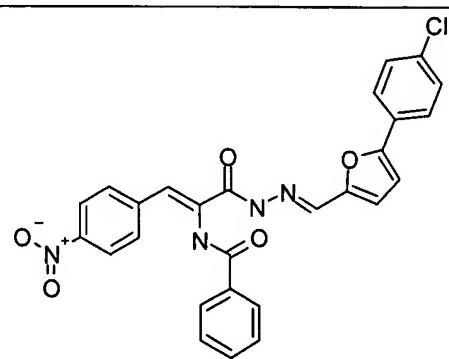
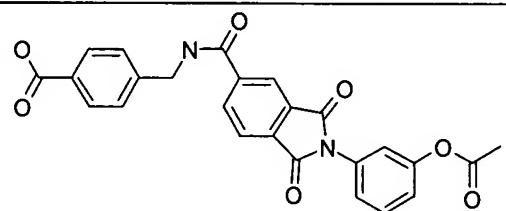
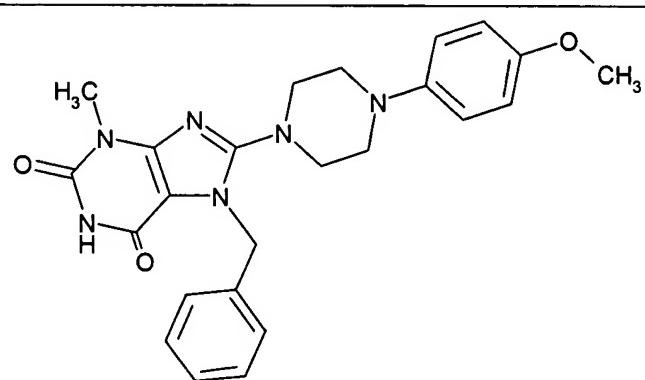
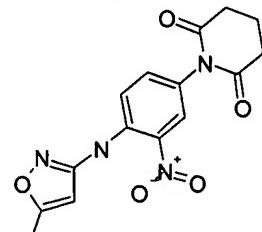
D4.006		4.2*
D4.007		6.9
D4.008		7.2*
D4.009		7.4
D4.010		7.5

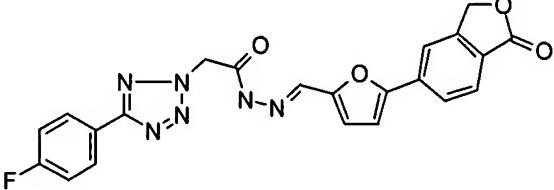
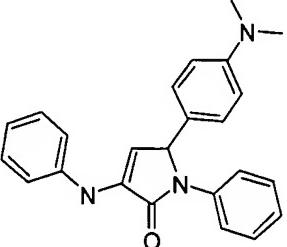
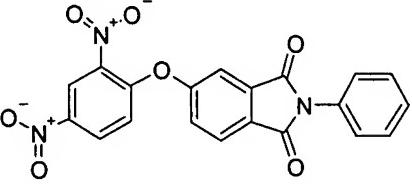
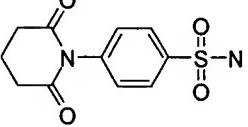
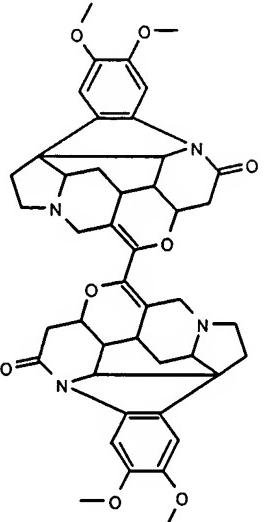
D4.011		8.5
D4.012		9.9
D4.013		10.1
D4.014		10.1
D4.015		12.2

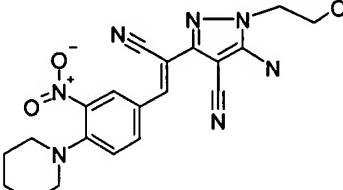
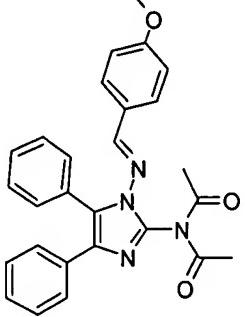
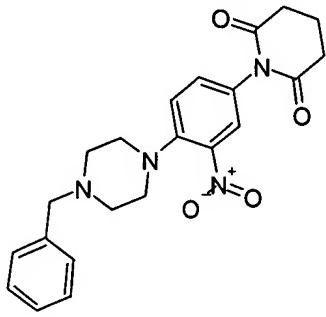
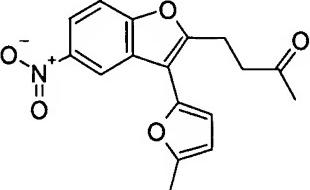
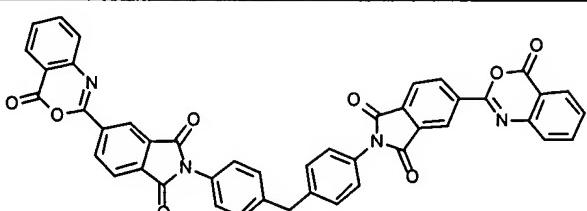
P29678.S01

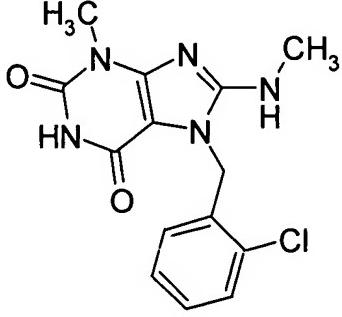
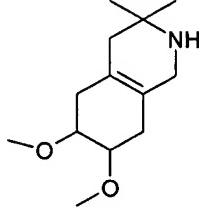
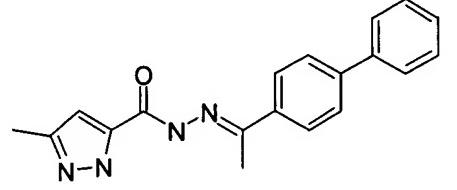
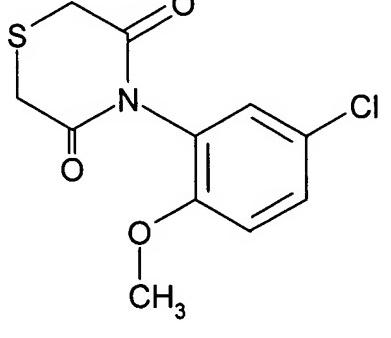
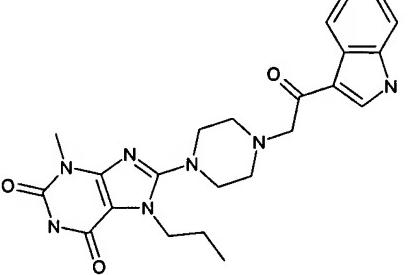
D4.016		12.3
D4.017		13.5
D4.018		14.4
D4.019		15.2
D4.020		15.2

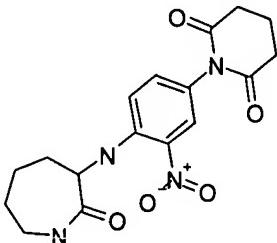
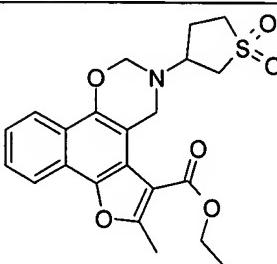
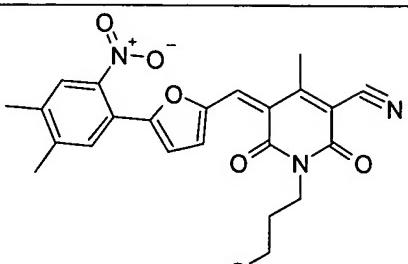
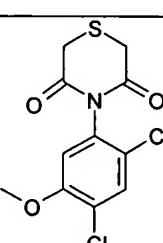
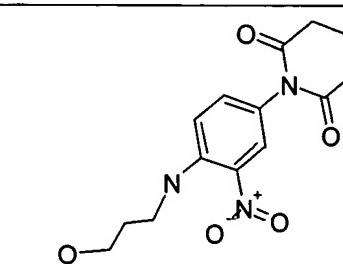
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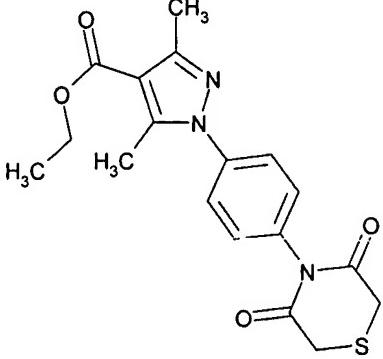
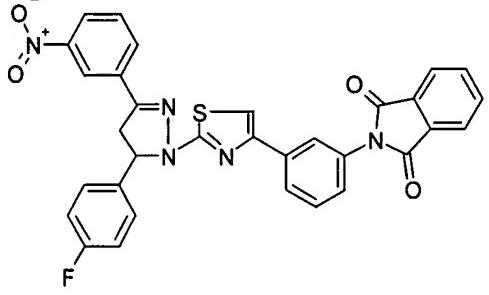
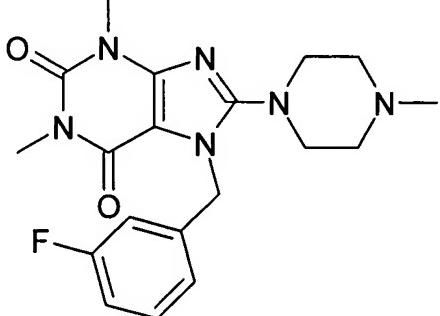
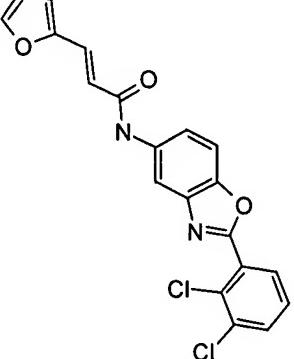
D4.021		15.4
D4.022		16.4
D4.023		18.2
D4.024		19.2
D4.025		20.0

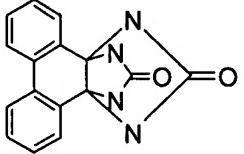
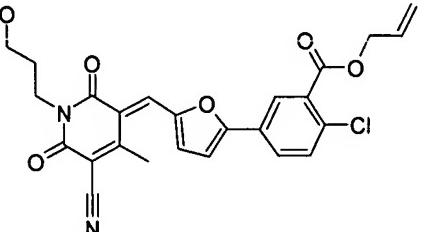
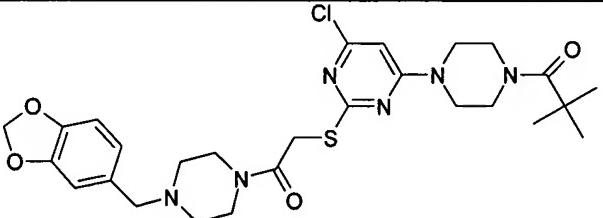
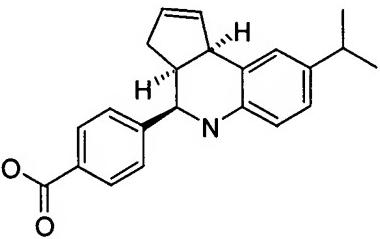
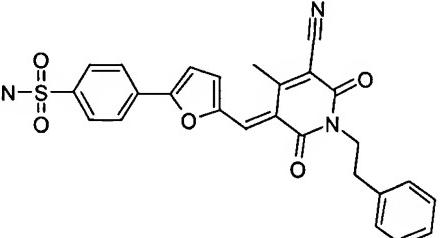
D4.026		20.3
D4.027		20.4
D4.028		20.6
D4.030		21.0
D4.031		22.9

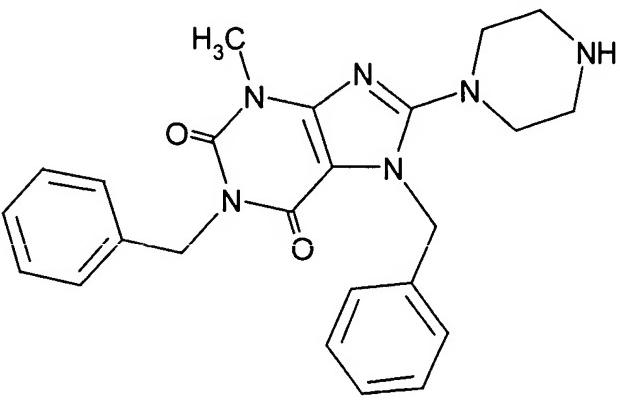
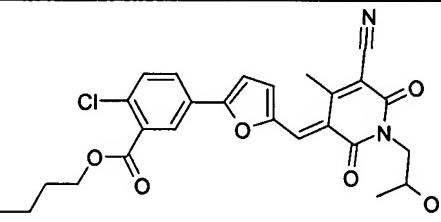
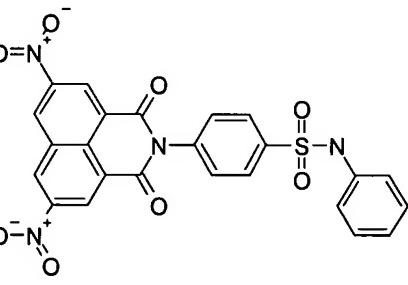
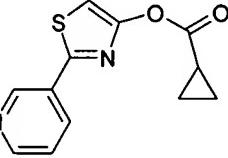
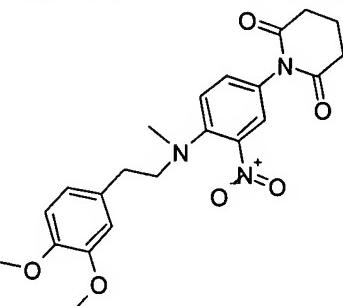
D4.032		23.6
D4.034		24.3
D4.035		24.5
D4.036		25.4
D4.037		27.7

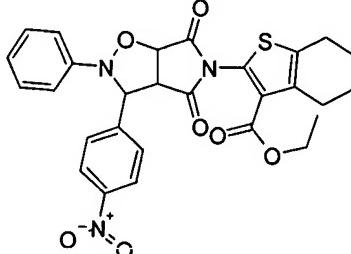
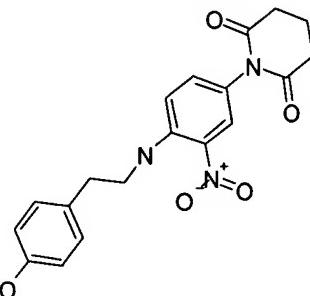
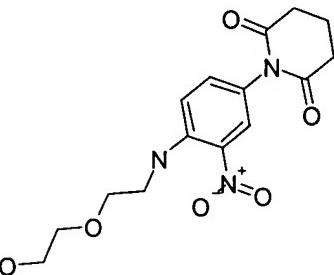
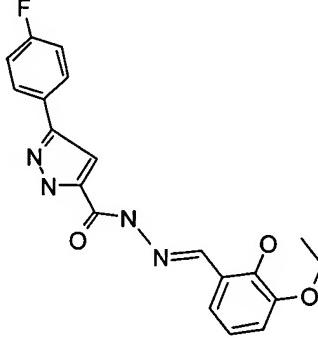
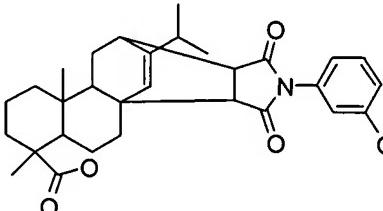
D4.038		27.8
D4.039		28.8
D4.040		29.8
D4.041		30.7
D4.042		30.8

D4.044		34.1
D4.045		34.2
D4.046		34.8
D4.047		35.3
D4.048		36.8

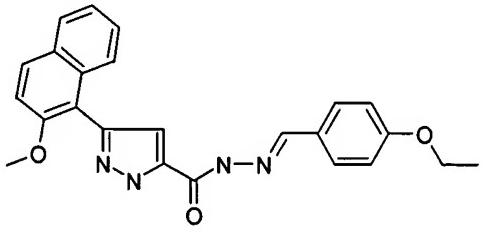
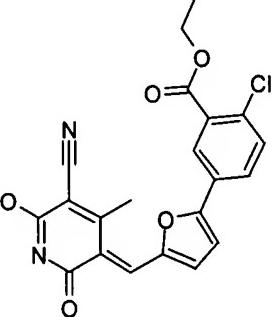
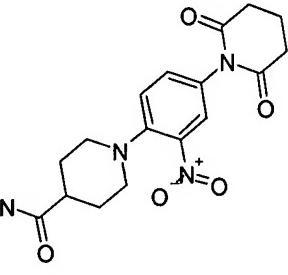
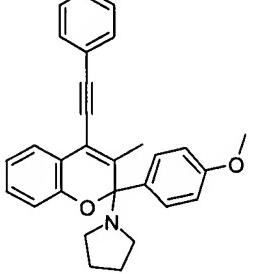
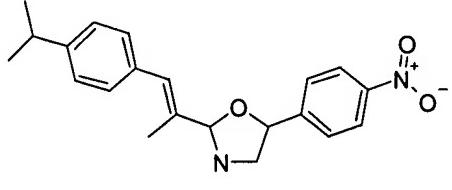
D4.049		37.4
D4.050		39.8
D4.051		41.2
D4.052		42.4

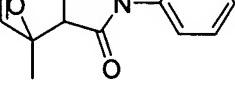
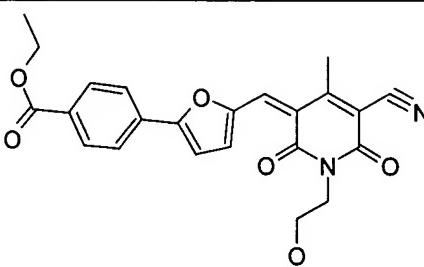
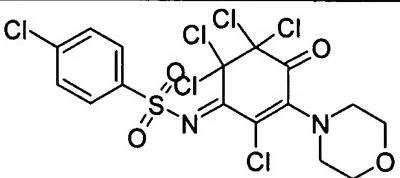
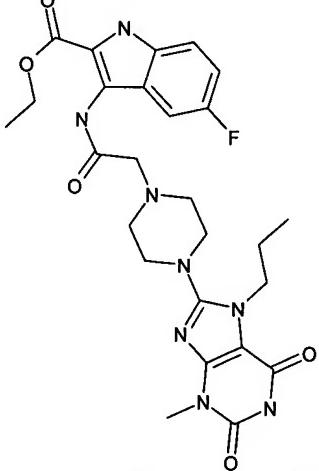
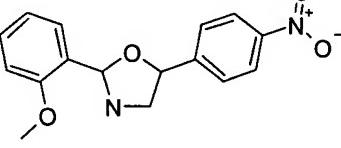
D4.053		43.1
D4.054		44.6
D4.055		45.6
D4.056		46.4
D4.057		48.2

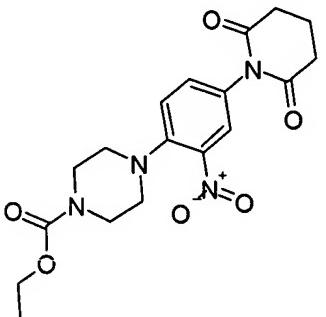
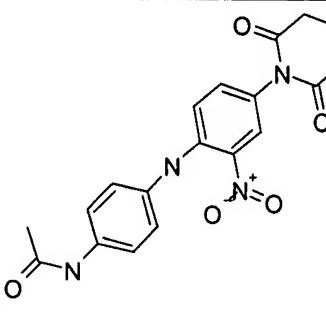
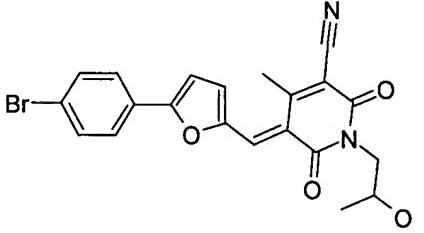
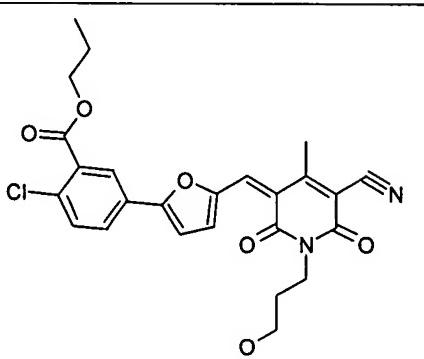
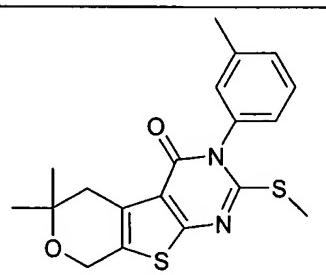
D4.058		48.3
D4.059		49.0
D4.060		49.4
D4.061		52.5
D4.062		52.6

D4.063		54.1
D4.064		54.9
D4.065		55.0
D4.066		55.3
D4.067		55.4

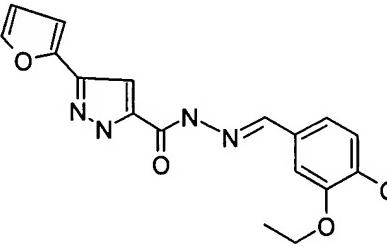
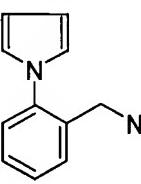
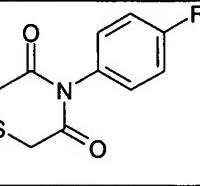
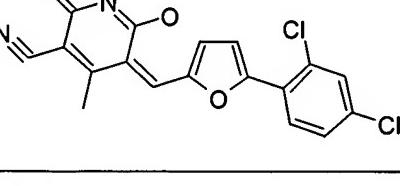
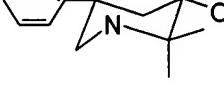
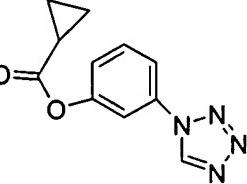
P29678.S01

D4.068		56.2
D4.069		56.7
D4.070		57.0
D4.071		60.7
D4.072		65.0

D4.073		65.6
D4.074		65.9
D4.075		66.6
D4.076		69.8*
D4.077		70.1

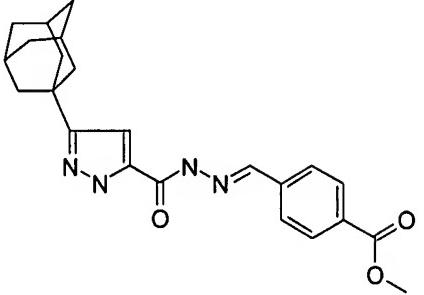
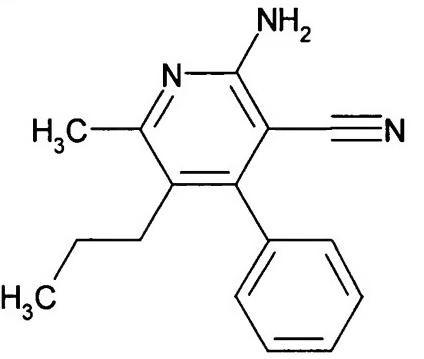
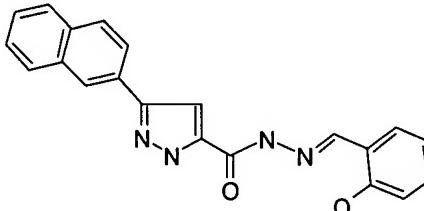
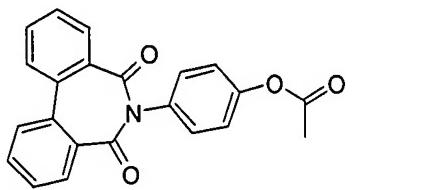
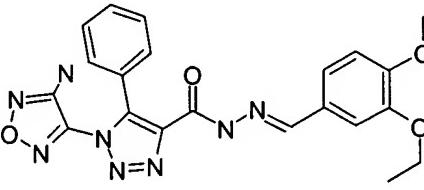
D4.078		70.4
D4.079		71.3*
D4.080		73.8
D4.081		76.3
D4.082		80.6

P29678.S01

D4.083		82.2
D4.084		84.9
D4.085		92.5
D4.086		94.5
D4.087		95.8
D4.088		96.2*
D4.089		98.4*

D4.090		110.0
D4.091		111.8*
D4.092		115.7
D4.093		138.3
D4.095		162.8*
D4.096		171.7*

D4.098		198.3*
D4.099		208.9*
D4.100		216.4*
D4.101		231.4*
D4.102		232.7*

D4.103		243.2*
D4.104		255.3*
D4.105		255.3*
D4.106		267.9*
D4.107		271.4*

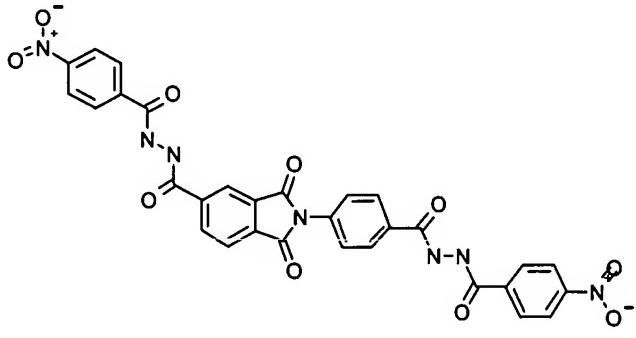
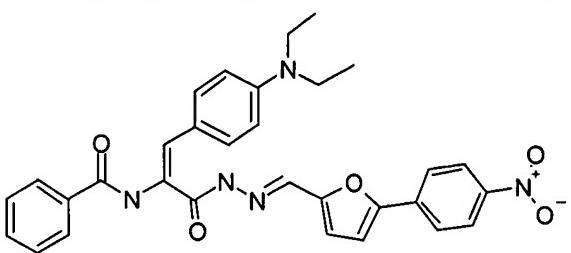
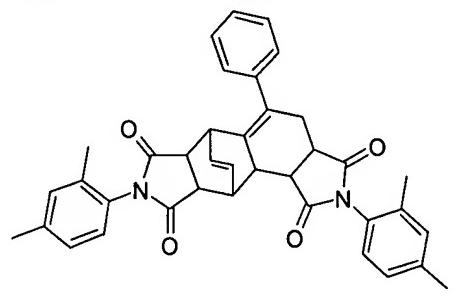
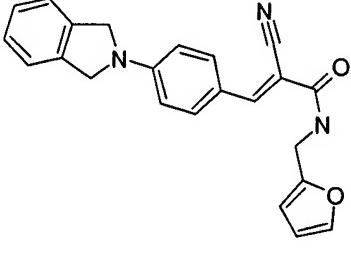
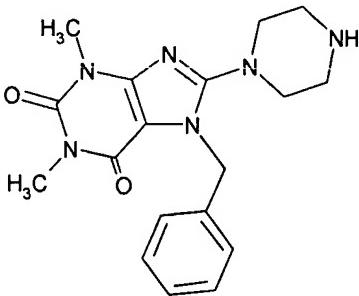
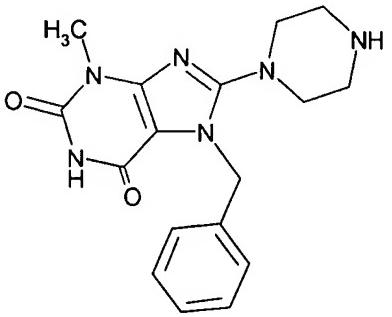
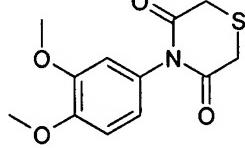
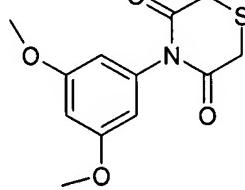
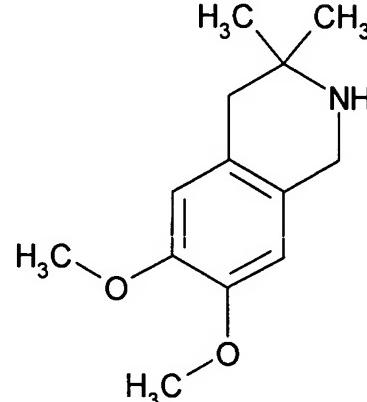
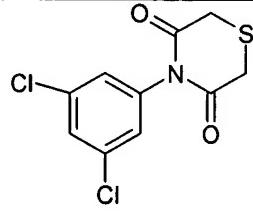
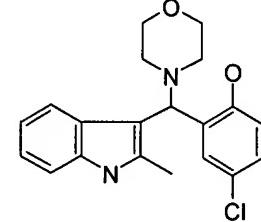
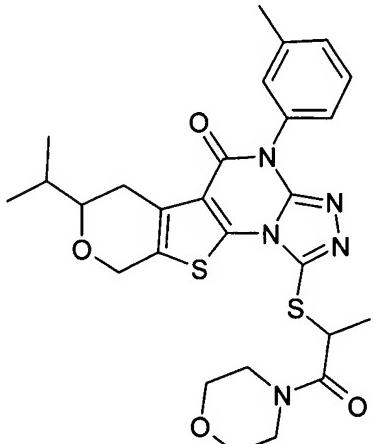
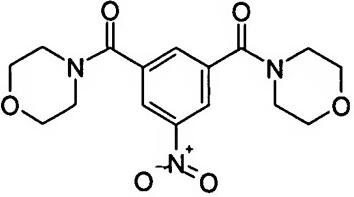
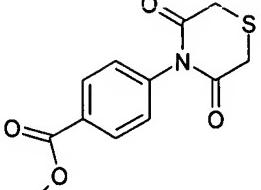
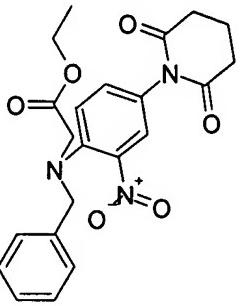
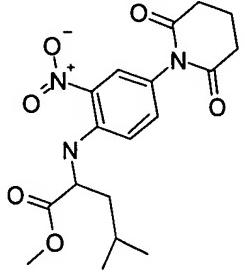
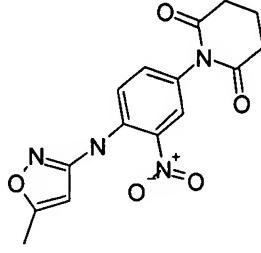
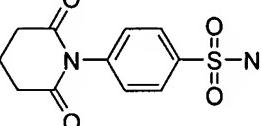
D4.115		401.9*
D4.116		417.9*
D4.117		527.4*
D4.118		456.1*

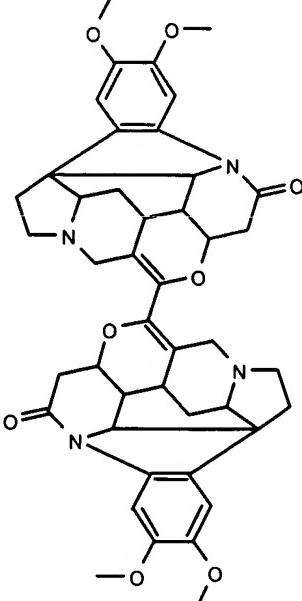
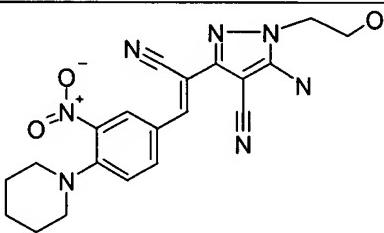
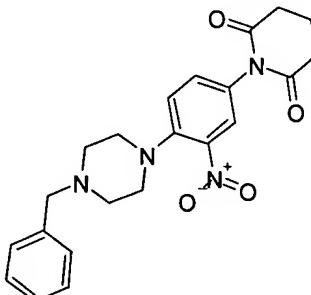
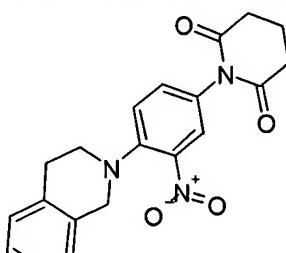
Table 5:

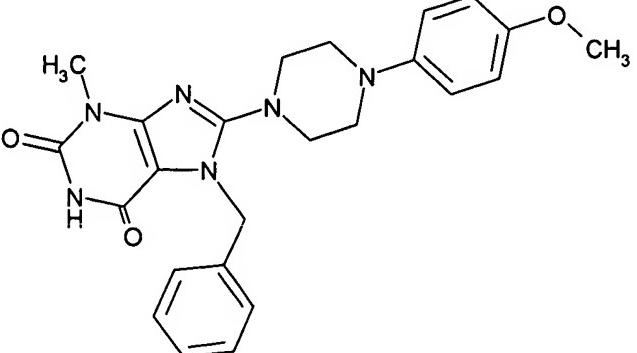
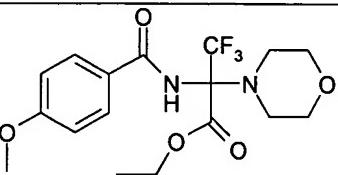
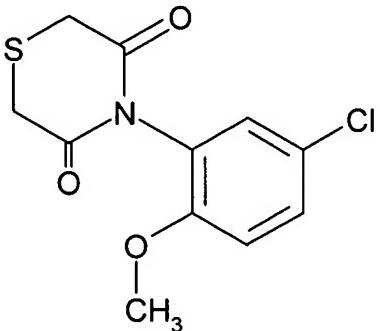
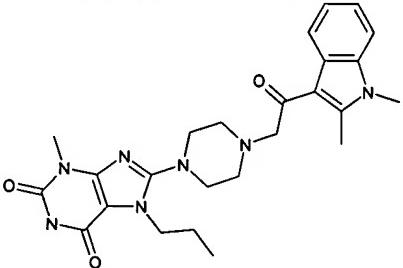
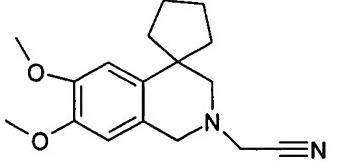
Compound ID.	Structure	IC50_{DPIV} [μM]
D5.001		0.4*
D5.002		0.8*
D5.003		3.1*
D5.004		3.8*

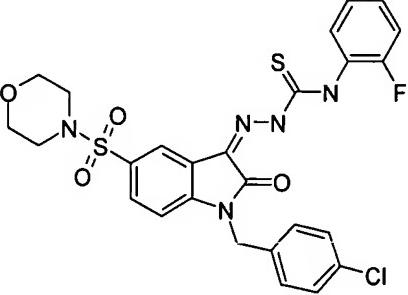
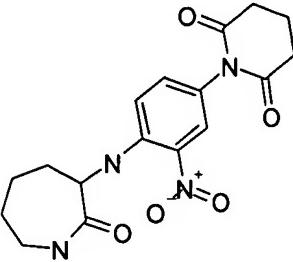
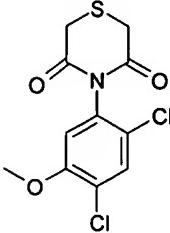
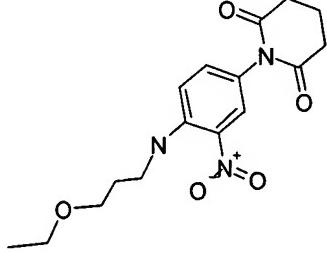
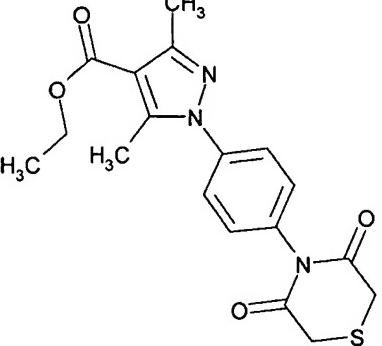
P29678.S01

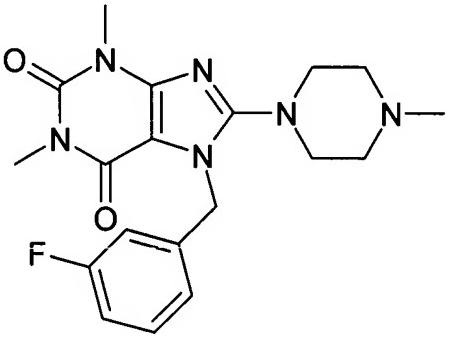
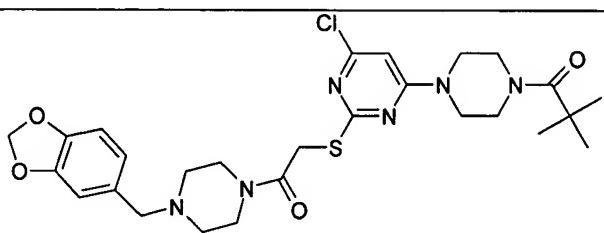
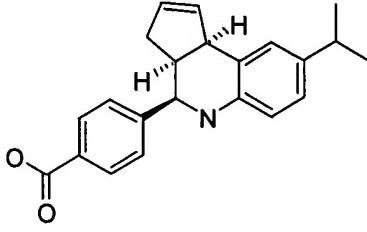
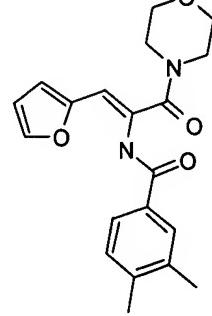
D5.005		6.0
D5.006		8.5
D5.007		12.1
D5.008		10.1

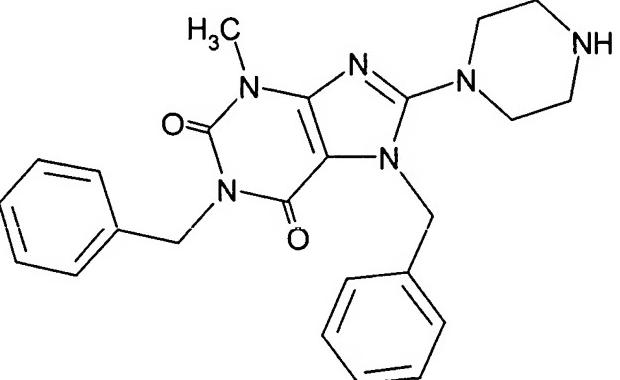
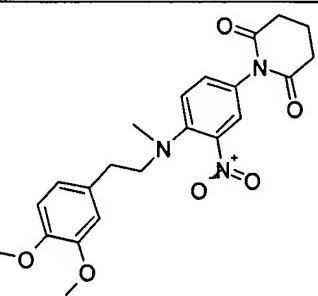
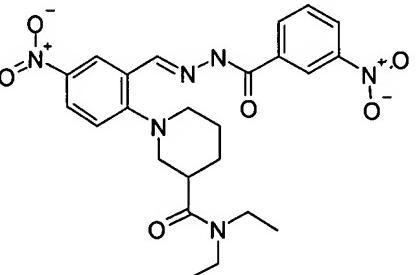
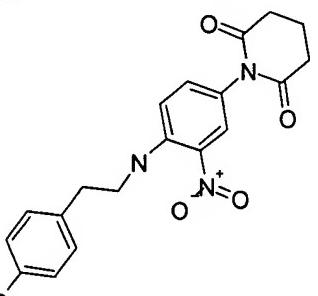
D5.009		10.7*
D5.010		12.2
D5.011		13.5
D5.013		15.4
D5.014		20.0
D5.015		21.0

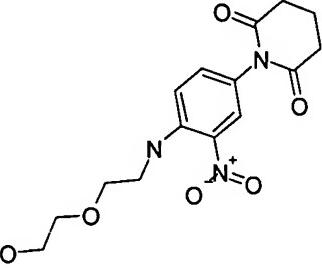
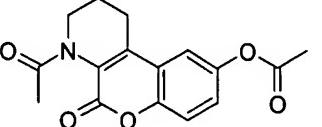
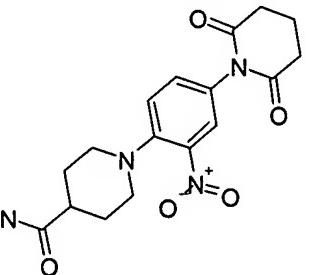
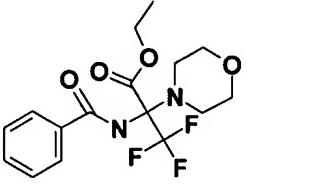
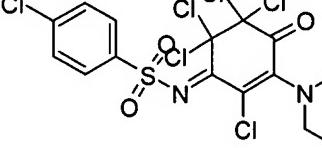
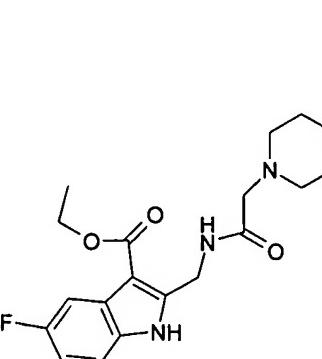
D5.016		22.9
D5.017		23.6
D5.018		24.5
D5.019		28.8

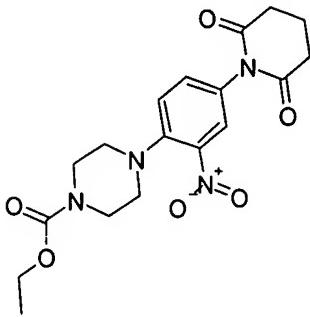
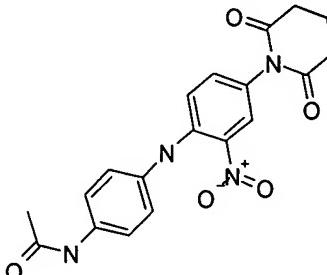
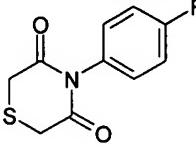
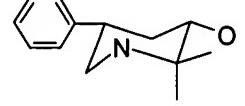
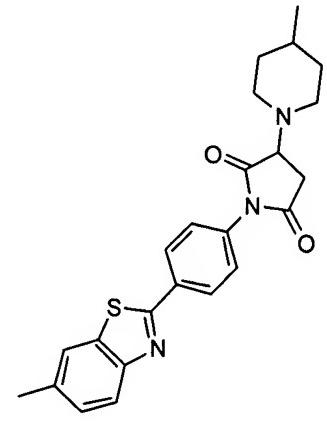
D5.020		19.2
D5.021		29.2
D5.022		30.7
D5.023		30.8
D5.024		31.4

D5.025		33.4
D5.026		34.1
D5.027		35.3
D5.028		36.8
D5.029		37.4

D5.030		41.2
D5.031		45.6
D5.032		46.4
D5.033		46.5

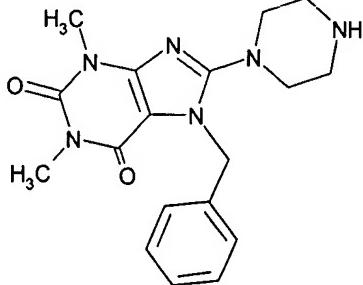
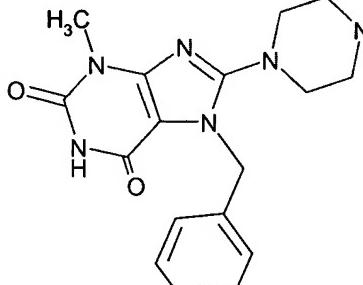
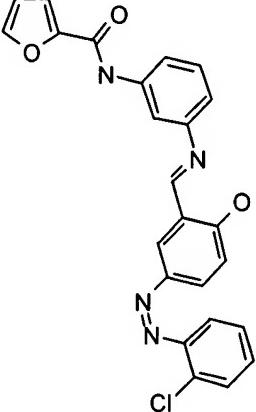
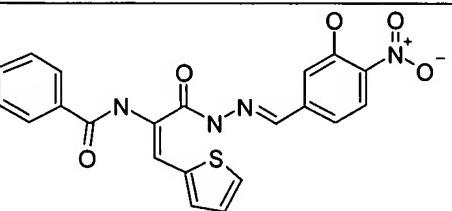
D5.034		48.3
D5.035		52.6
D5.036		54.0
D5.037		54.8

D5.038		55.0
D5.039		59.4
D5.040		57.0
D5.041		61.9
D5.042		66.6
D5.043		69.8*

D5.044		70.4
D5.045		71.3*
D5.046		94.5
D5.047		96.6*
D5.048		115.7

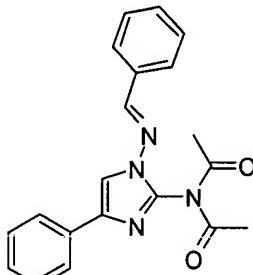
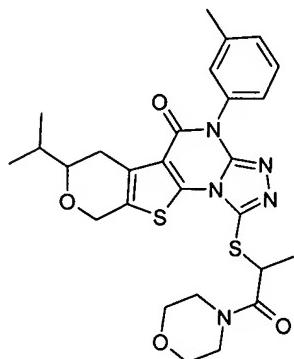
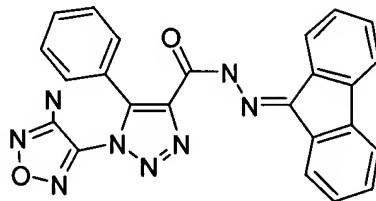
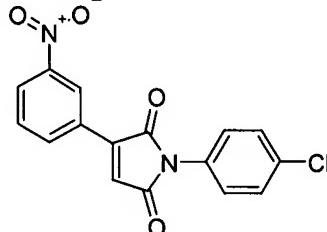
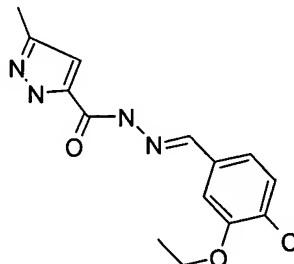
D5.050		216.4*
D5.051		232.7*
D5.052		279.4*
D5.053		361.1*

Table 6:

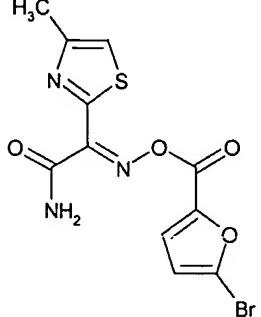
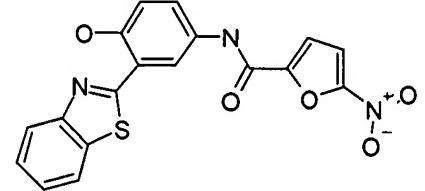
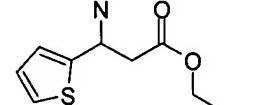
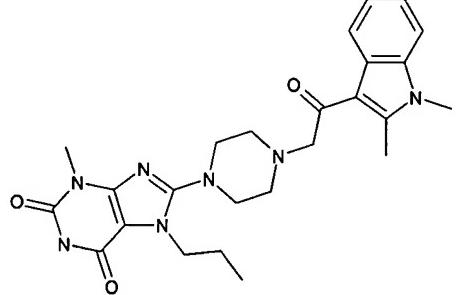
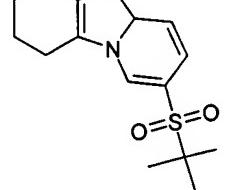
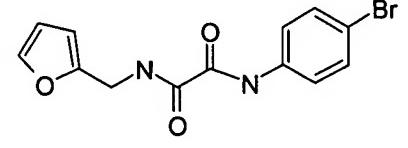
Compound ID.	Structure	IC50DPIV [μM]
D6.001		0.4*
D6.002		0.8*
D6.003		2.5*
D6.004		6.5

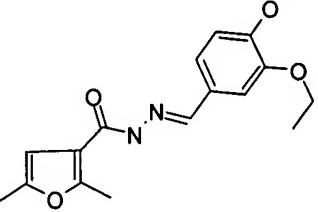
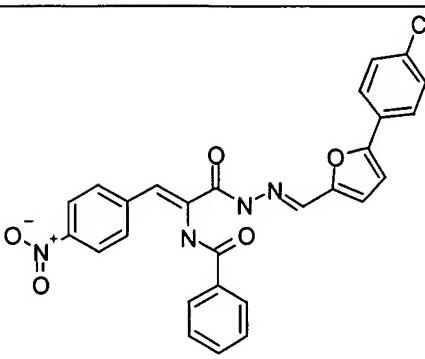
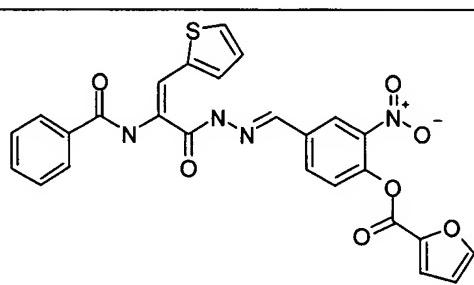
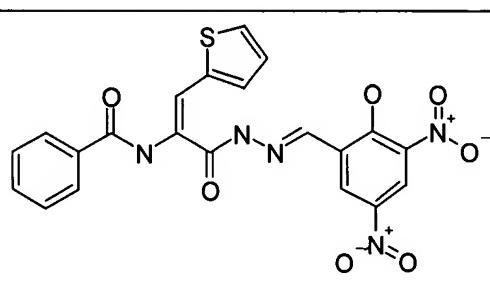
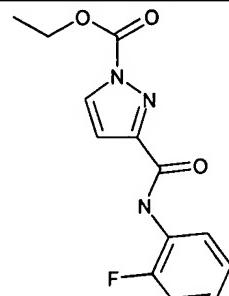
P29678.S01

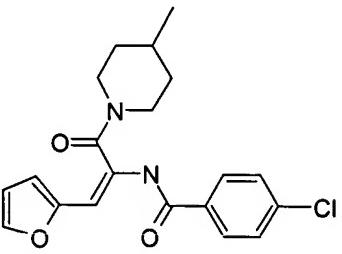
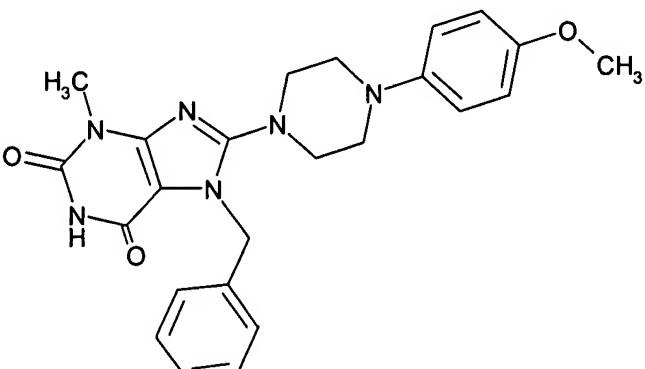
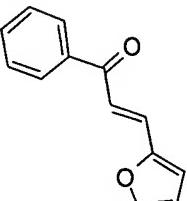
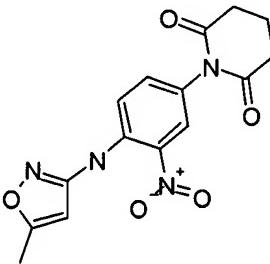
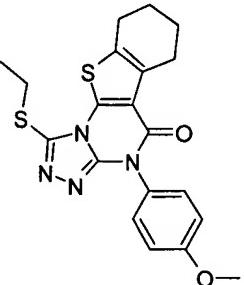
D6.006		7.5
D6.007		7.5
D6.008		7.5
D6.009		8.1
D6.010		9.2

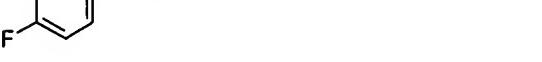
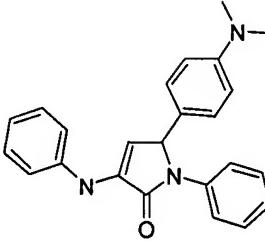
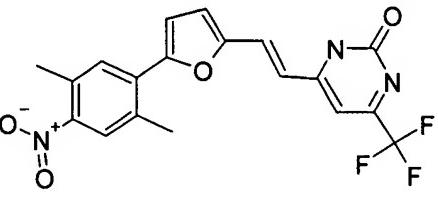
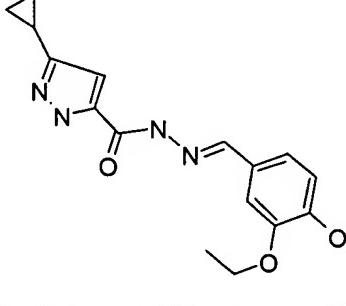
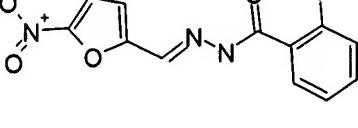
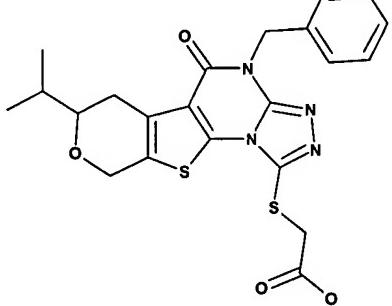
D6.011		9.9
D6.012		10.1
D6.013		10.1
D6.014		12.3
D6.015		13.6

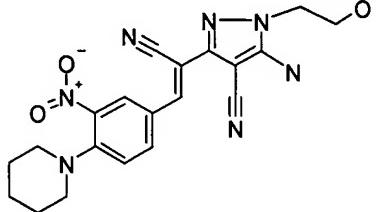
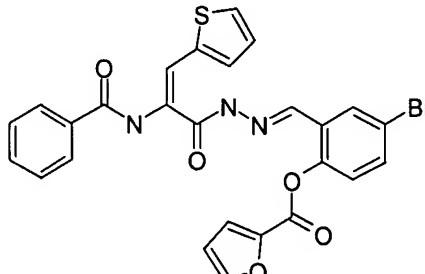
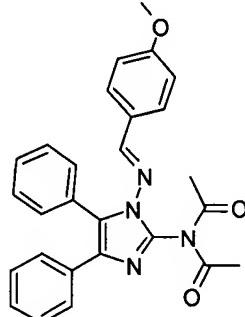
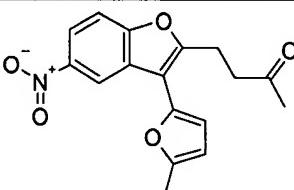
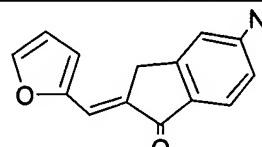
P29678.S01

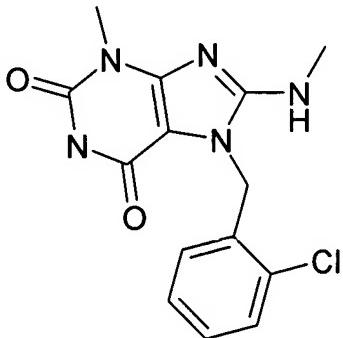
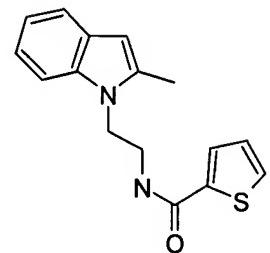
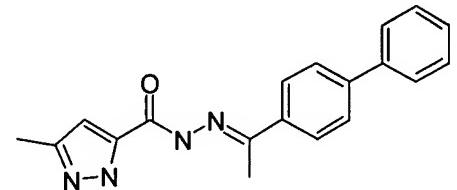
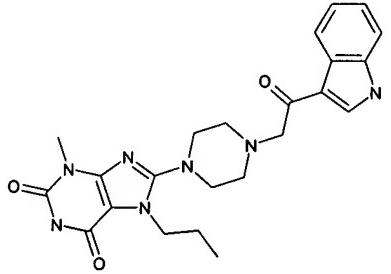
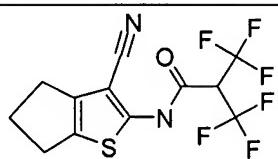
D6.016		14.0
D6.017		14.4
D6.018		15.2
D6.019		15.2
D6.020		15.6
D6.021		16.1

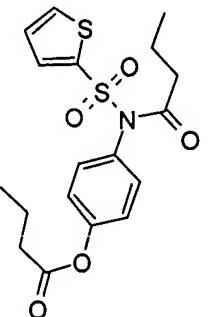
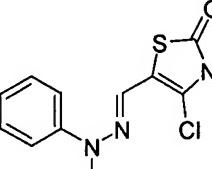
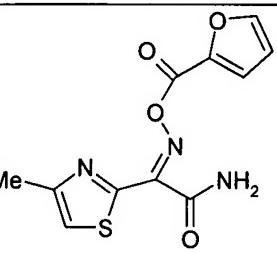
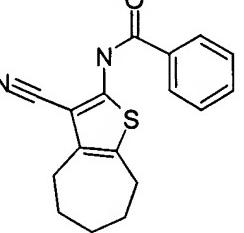
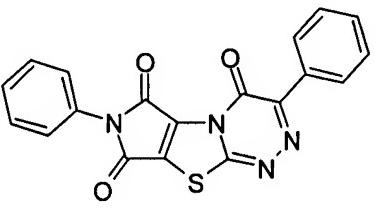
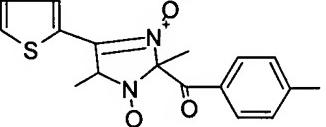
D6.022		16.2
D6.023		16.4
D6.024		16.7
D6.025		17.5
D6.026		17.9

D6.027		18.5
D6.028		19.2
D6.029		19.7
D6.030		20.0
D6.031		20.2

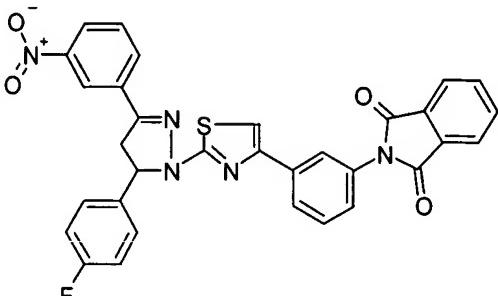
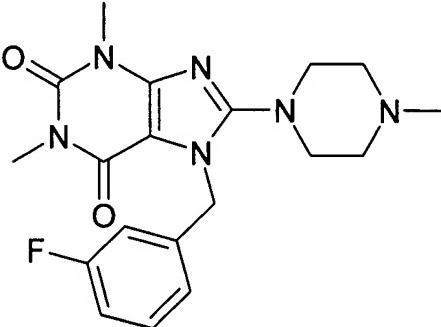
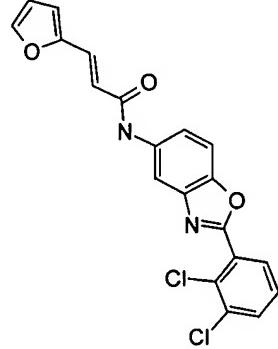
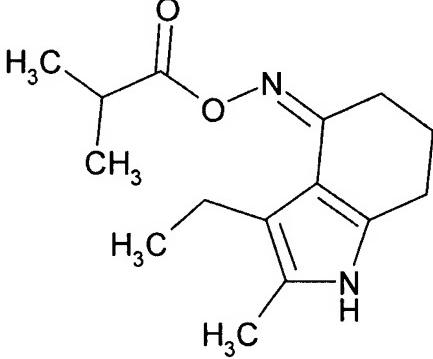
D6.032		20.3
D6.033		20.4
D6.034		20.6
D6.035		20.8
D6.036		20.9
D6.037		18.9

D6.038		23.6
D6.039		24.1
D6.040		24.3
D6.041		25.4
D6.042		27.5

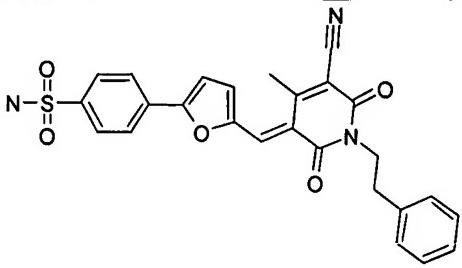
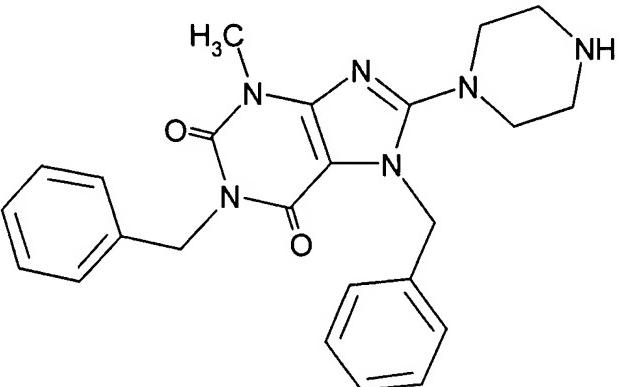
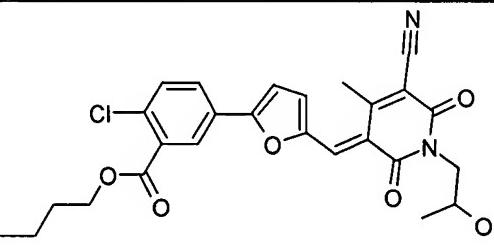
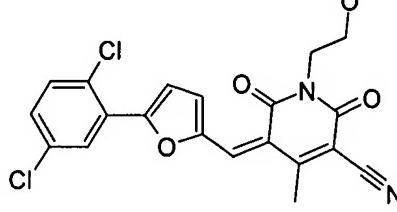
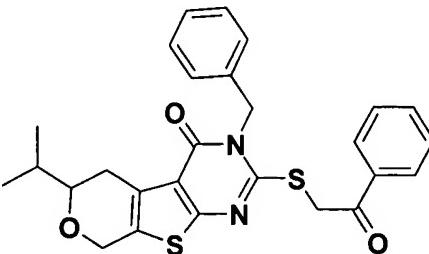
D6.043		27.8
D6.044		28.8
D6.045		29.8
D6.046		30.8
D6.047		30.9

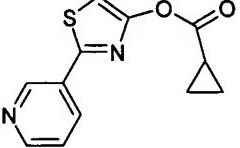
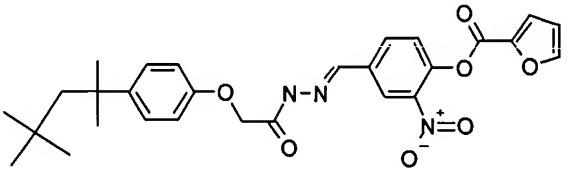
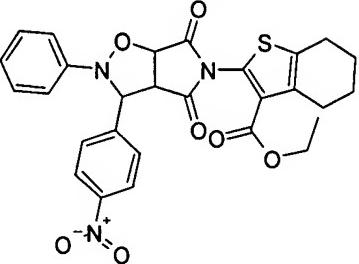
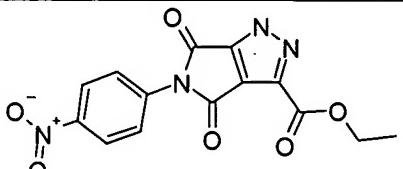
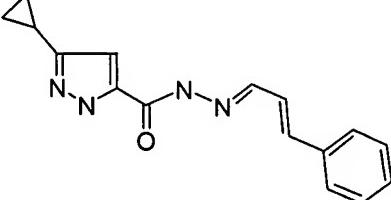
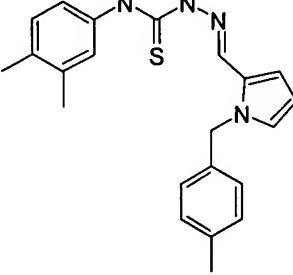
D6.048		31.3
D6.049		32.4
D6.050		32.8
D6.051		33.0
D6.052		332.3*
D6.053		34.1

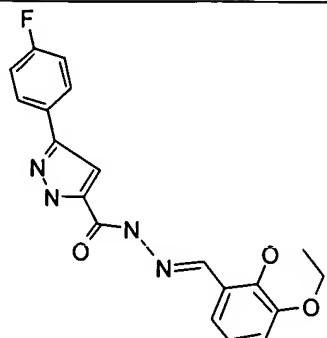
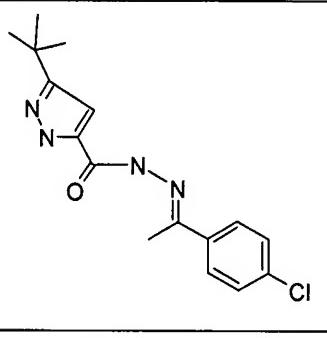
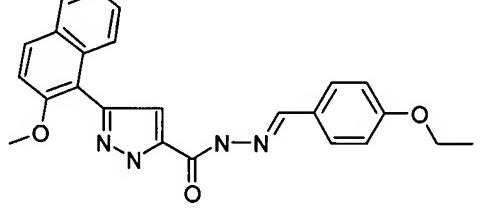
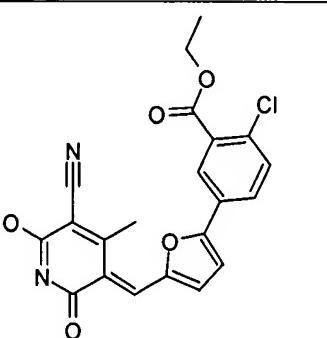
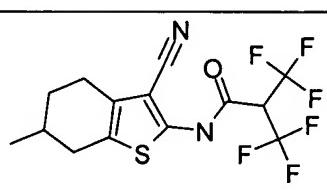
D6.054		34.2
D6.055		34.8
D6.056		37.4
D6.057		38.1
D6.058		39.5

D6.059		39.8
D6.060		41.2
D6.061		42.4
D6.062		43.8

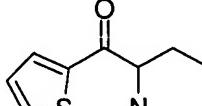
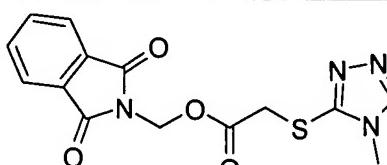
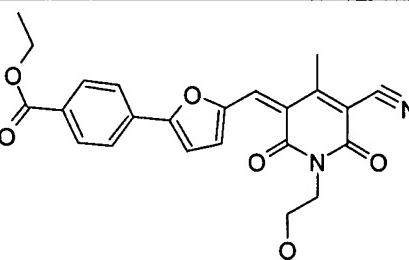
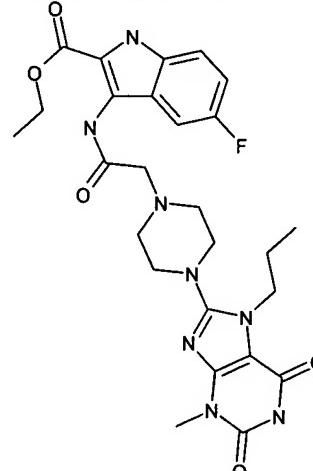
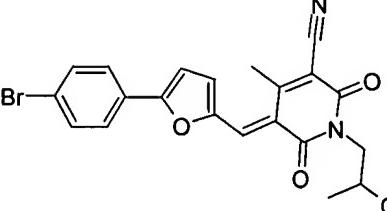
D6.063		44.0
D6.064		44.3
D6.065		44.6
D6.066		46.0
D6.067		46.5

D6.068		48.2
D6.069		48.3
D6.070		49.0
D6.071		51.7
D6.072		52.4

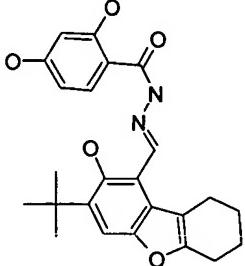
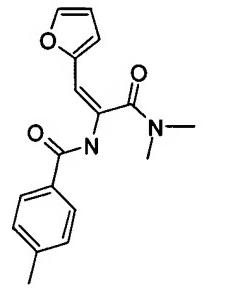
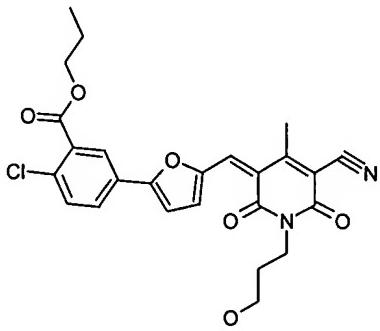
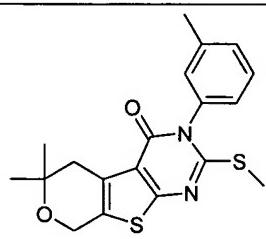
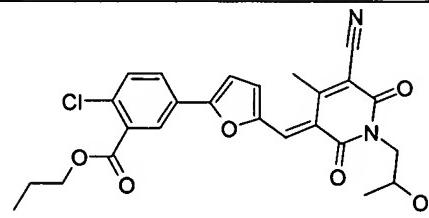
D6.073		52.5
D6.074		52.9
D6.075		54.1
D6.076		54.5
D6.077		55.0
D6.078		55.2

D6.079		55.3
D6.080		55.7
D6.081		56.3
D6.082		56.7
D6.083		59.8

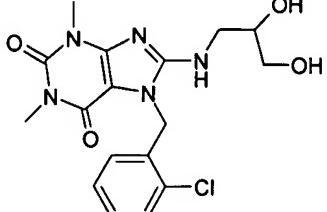
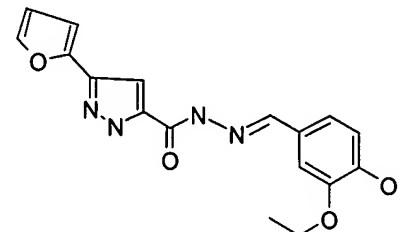
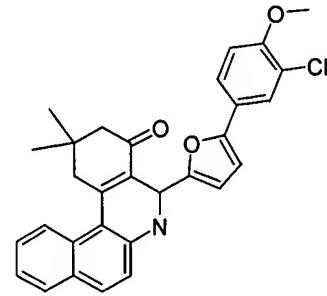
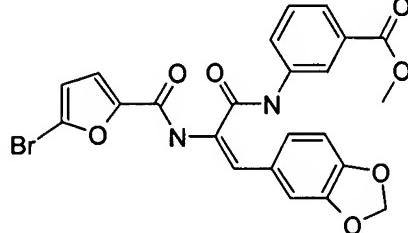
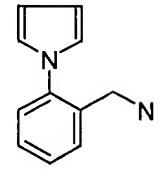
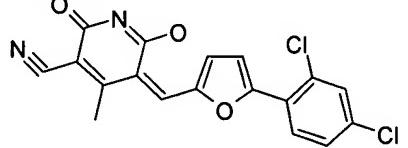
P29678.S01

D6.084		57.4
D6.085		61.4
D6.086		62.4
D6.087		65.9
D6.088		69.8*
D6.089		73.8

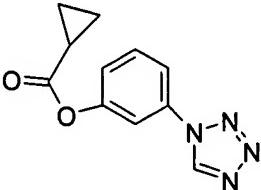
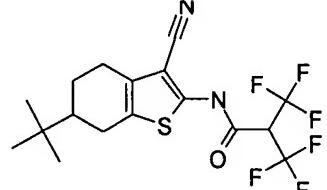
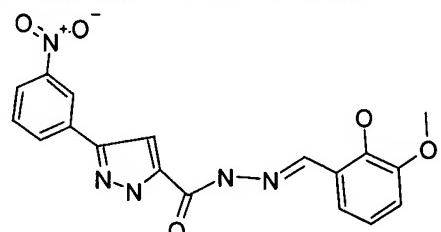
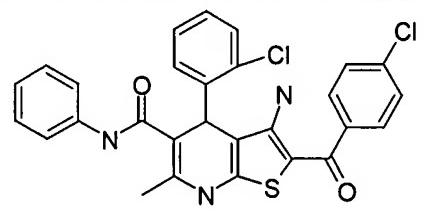
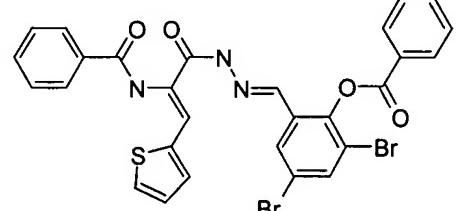
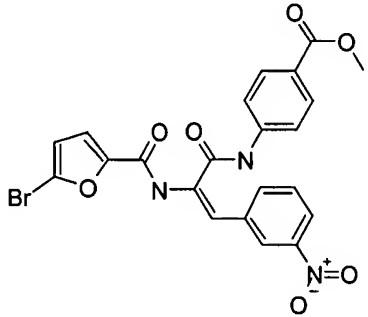
P29678.S01

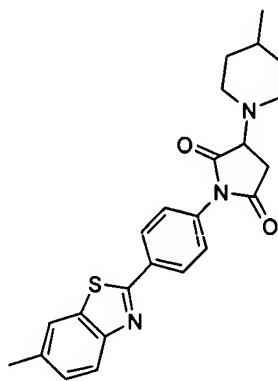
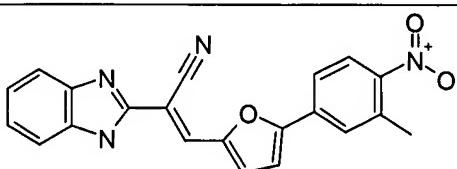
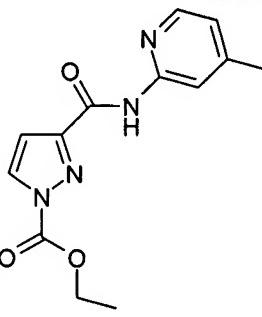
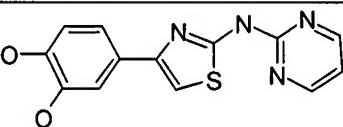
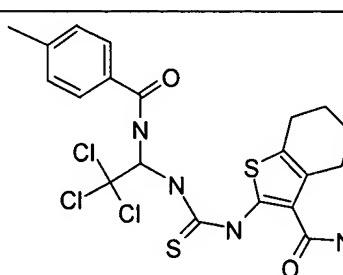
D6.090		74.7*
D6.091		47.7
D6.092		76.3
D6.094		80.6
D6.095		82.2

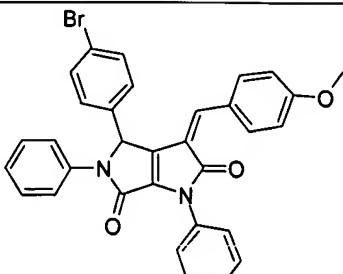
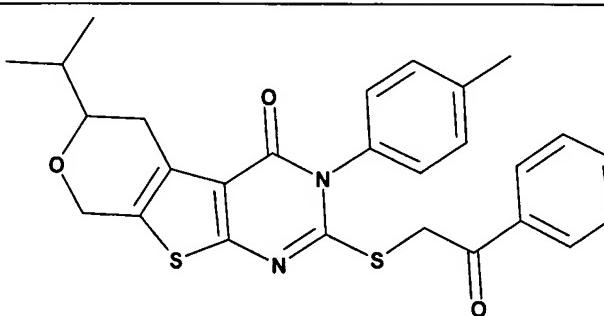
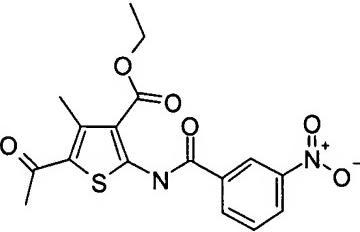
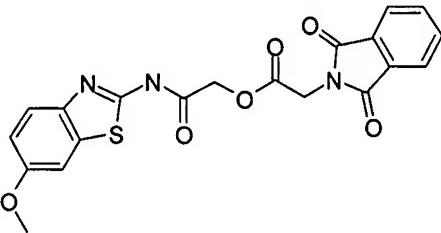
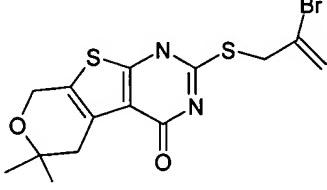
P29678.S01

D6.096		83.3*
D6.097		84.9
D6.098		87.9
D6.099		92.2*
D6.100		92.5
D6.101		95.8

P29678.S01

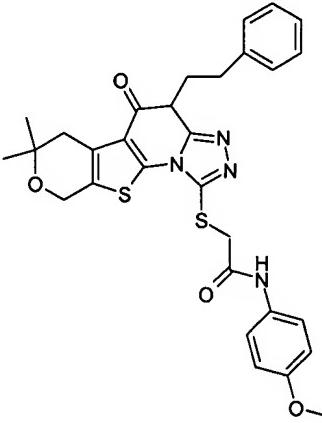
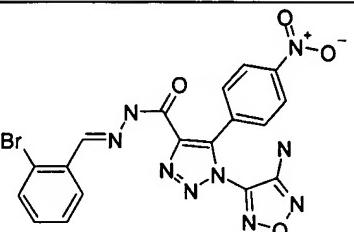
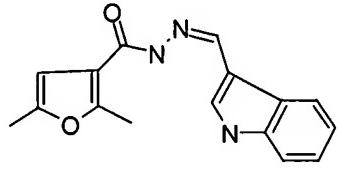
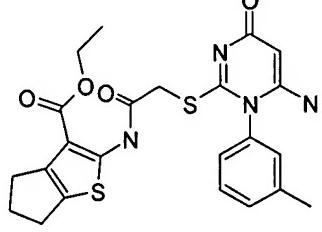
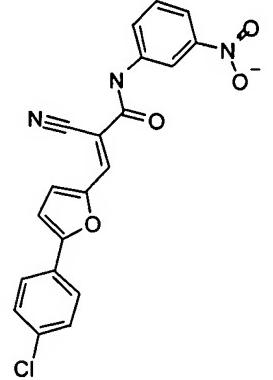
D6.102		98.4*
D6.103		100.6
D6.105		110.0
D6.106		111.8*
D6.107		113.8*
D6.108		115.0

D6.110		115.7
D6.111		138.3
D6.112		148.4*
D6.113		162.8*
D6.114		168.9*

D6.115		198.3*
D6.116		208.9*
D6.117		215.2*
D6.118		224.1*
D6.119		237.0*

D6.120		243.2*
D6.121		251.7*
D6.122		251.7*
D6.123		255.3*
D6.124		269.0*
D6.125		271.4*

P29678.S01

D6.126		283.7*
D6.127		314.0*
D6.129		339.7*
D6.130		362.6*
D6.131		394.3*

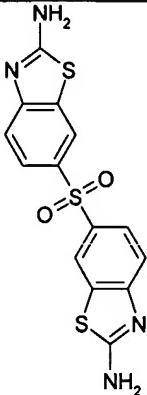
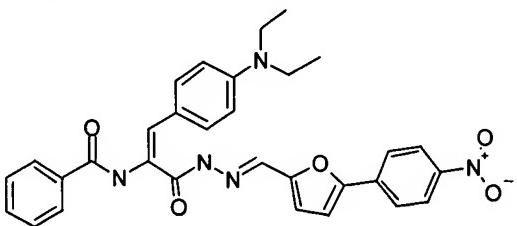
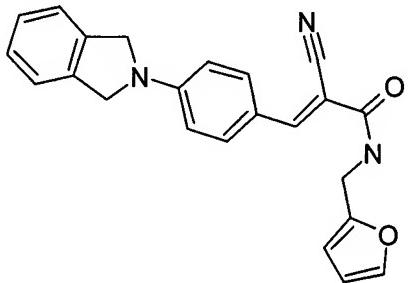
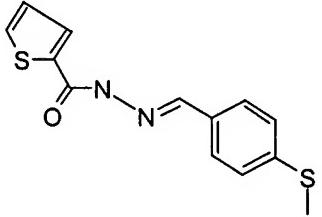
D6.132		416.9*
D6.133		417.9*
D6.134		456.1*
D6.135		498.0*

Table 7:

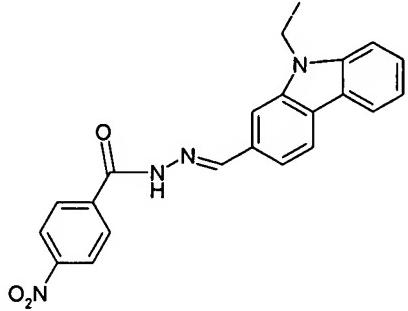
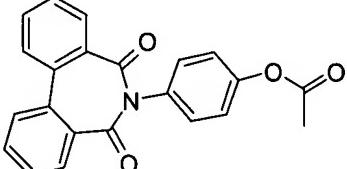
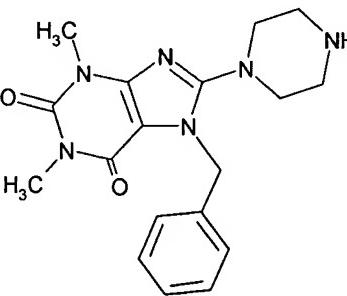
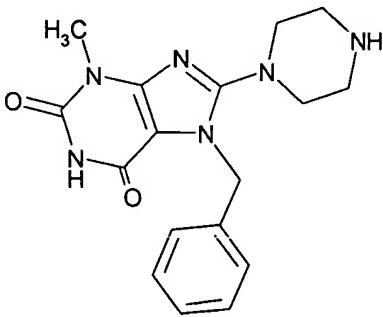
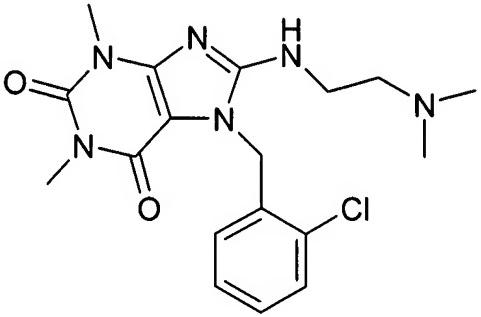
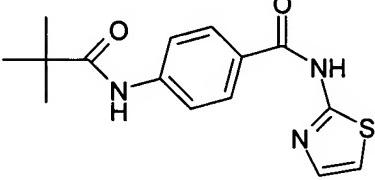
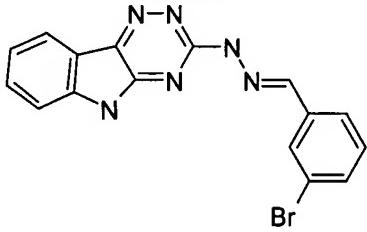
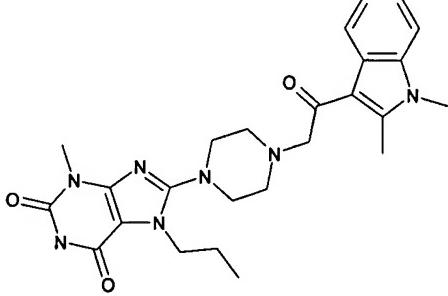
Compound ID.	Structure	IC50_{DPIV} [μM]
D7.001		165.3*
D7.003		267.9*

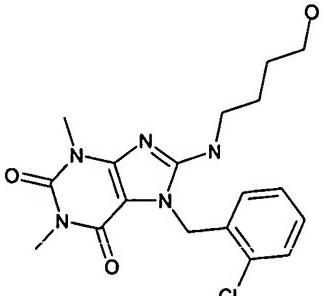
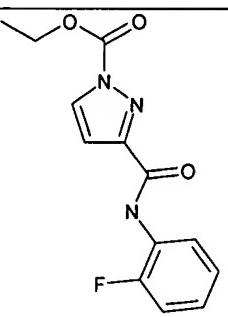
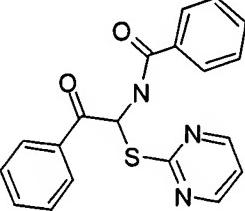
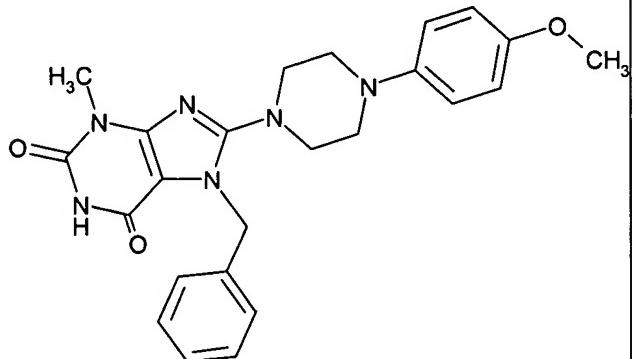
Table 8:

Compound ID.	Structure	IC50_{DPIV} [nM]
D8.001		0.4*

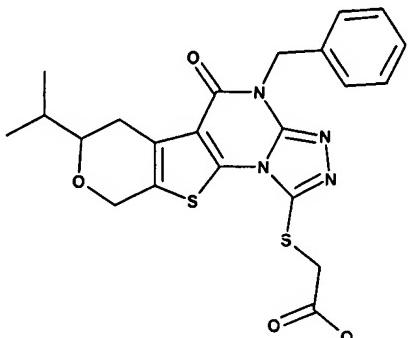
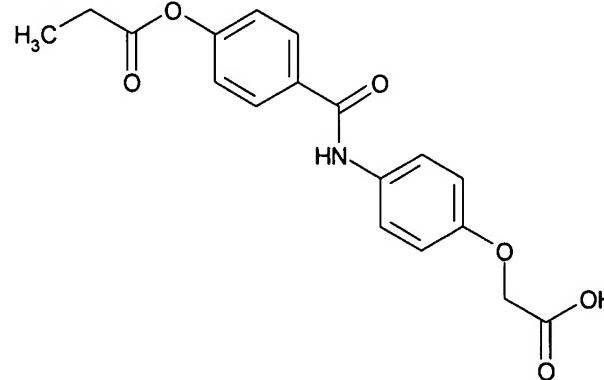
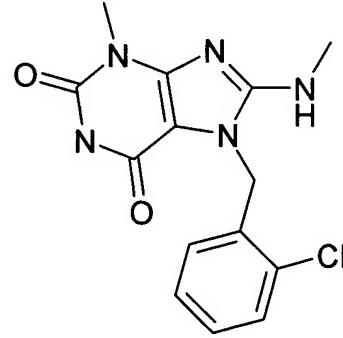
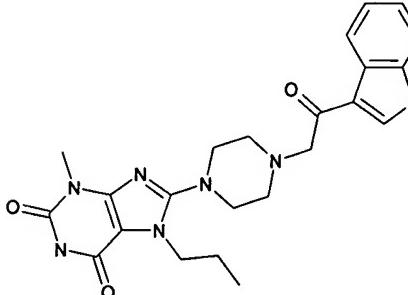
P29678.S01

D8.002		0.8*
D8.003		7.5
D8.004		7.5
D8.005		12.2
D8.006		15.2

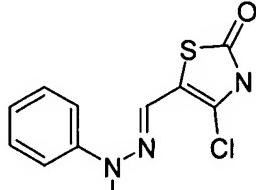
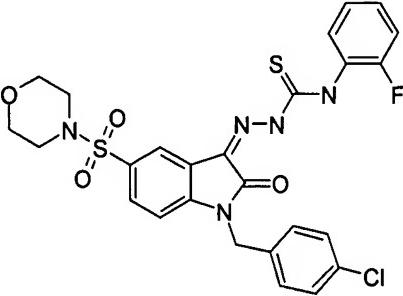
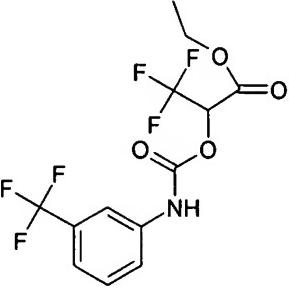
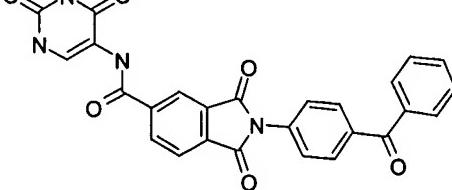
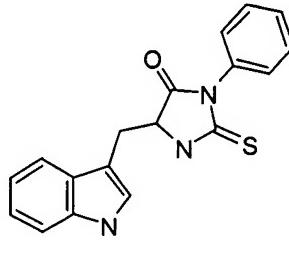
P29678.S01

D8.007		16.2
D8.008		17.9
D8.009		18.2
D8.010		19.2

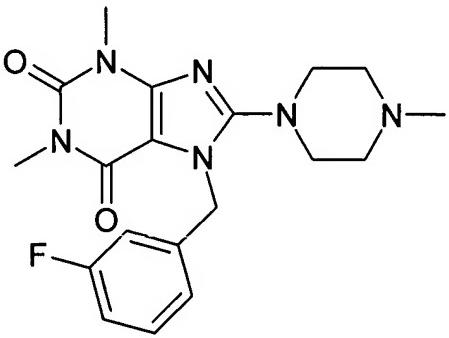
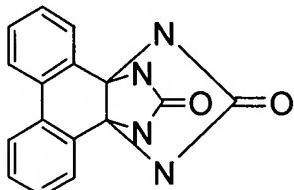
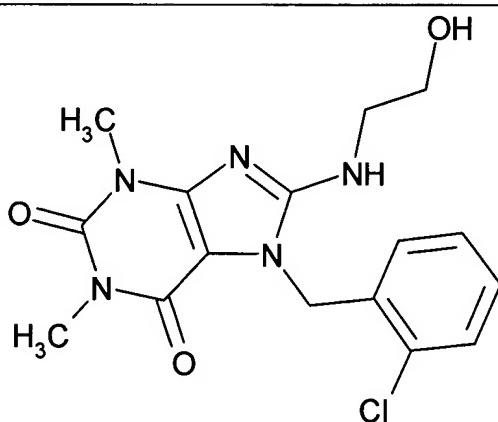
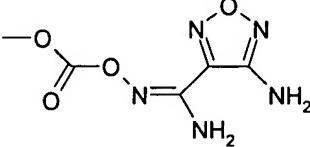
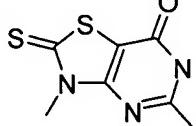
P29678.S01

D8.011		18.9
D8.012		23.8
D8.013		27.8
D8.014		30.8

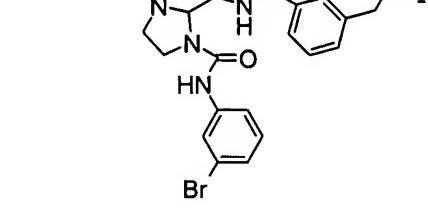
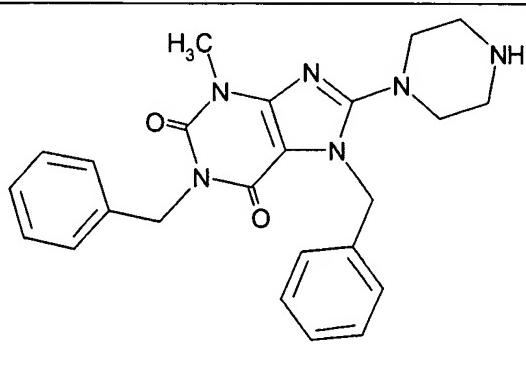
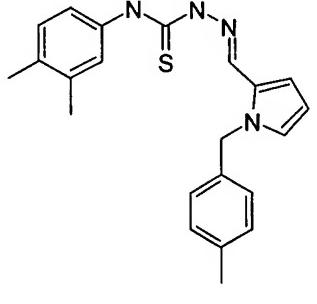
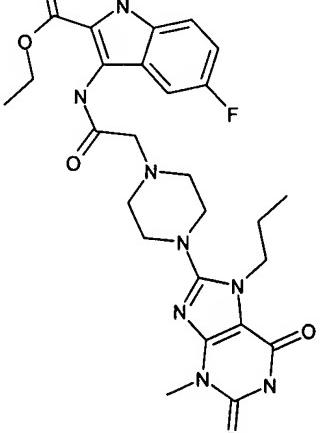
P29678.S01

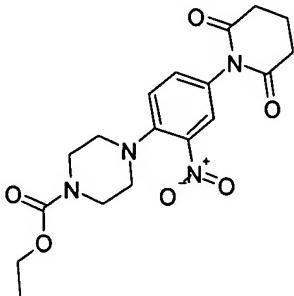
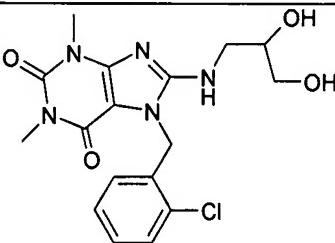
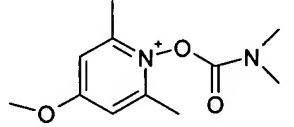
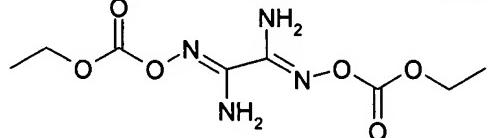
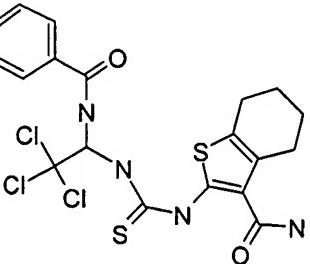
D8.015		32.4
D8.016		33.4
D8.017		33.3
D8.018		38.2
D8.019		40.2

P29678.S01

D8.020		41.2
D8.021		43.1
D8.022		44.0
D8.023		44.3
D8.024		46.0

P29678.S01

D8.025		46.3
D8.026		48.3
D8.027		55.2
D8.028		69.8*

D8.029		70.4
D8.030		83.3*
D8.031		118.9*
D8.032		132.7*
D8.033		168.9*

P29678.S01

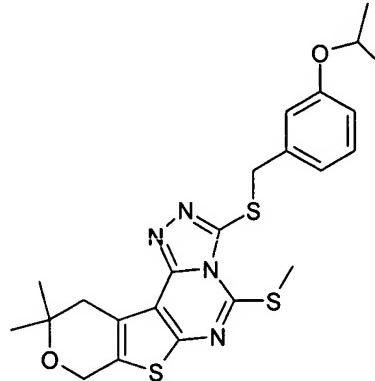
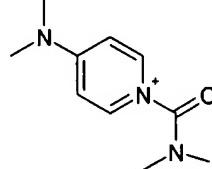
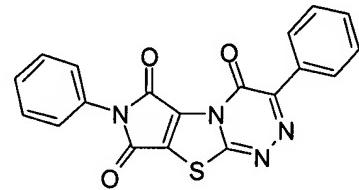
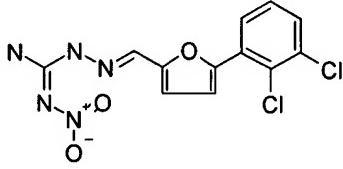
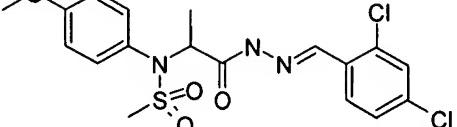
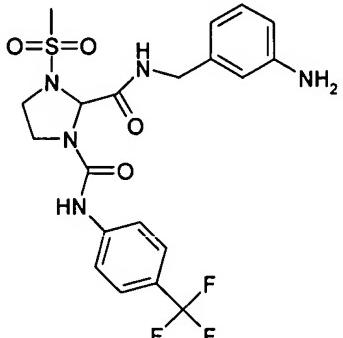
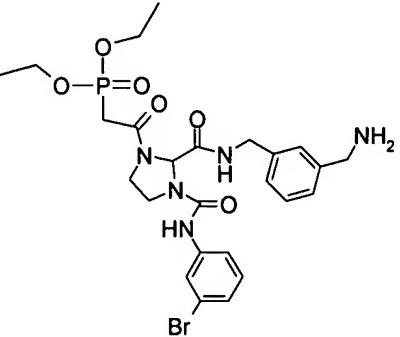
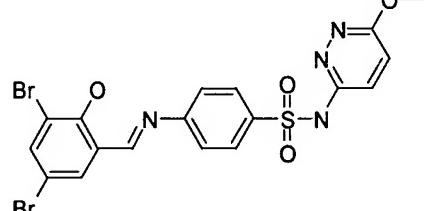
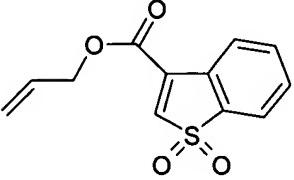
D8.034		269.0*
D8.035		283.6*
D8.037		332.3*
D8.038		609.2*

Table 9:

Compound ID.	Structure	IC50DPIV [μM]
D9.001		2.9*

P29678.S01

D9.007		40.5
D9.008		46.3
D9.010		88.8
D9.011		251.7*

P29678.S01

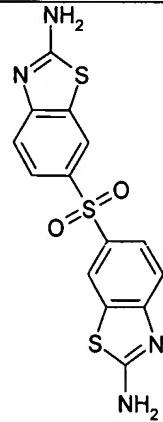
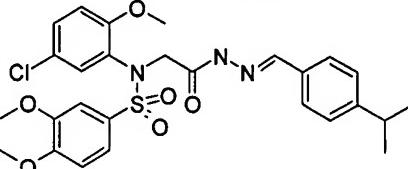
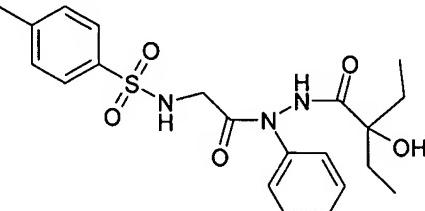
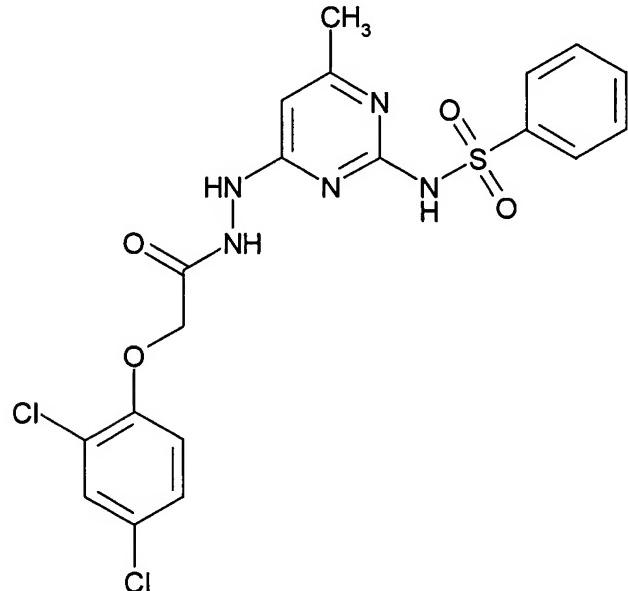
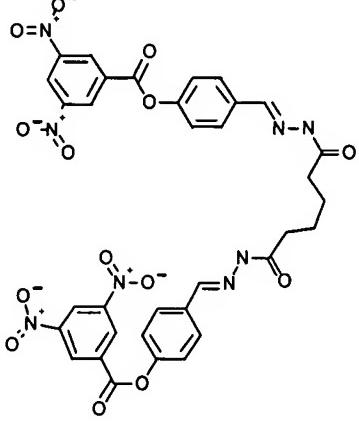
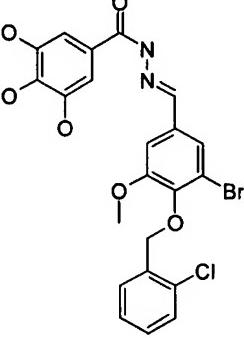
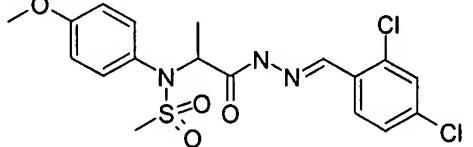
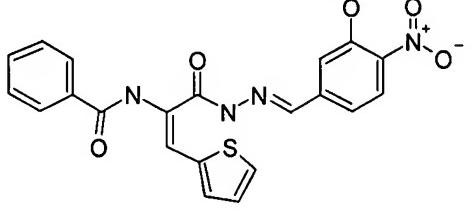
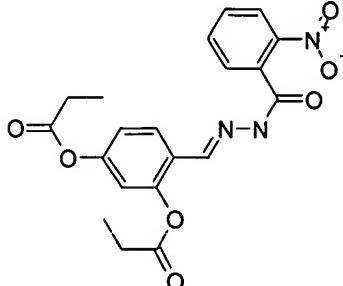
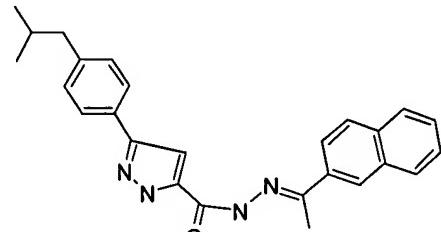
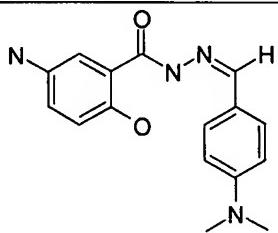
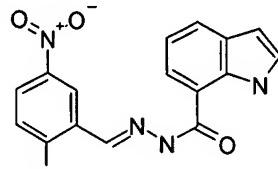
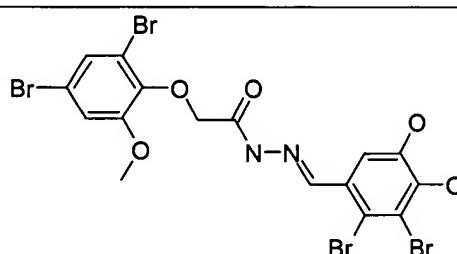
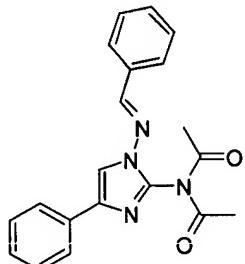
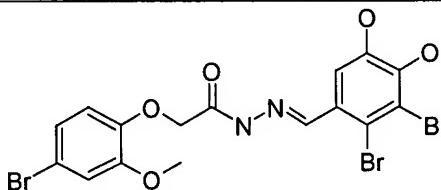
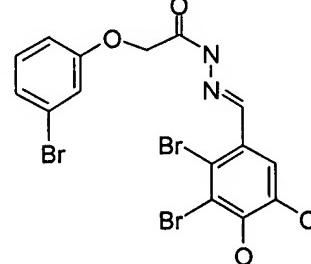
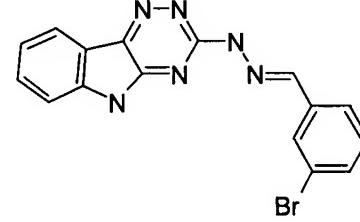
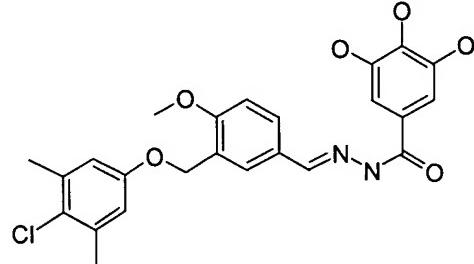
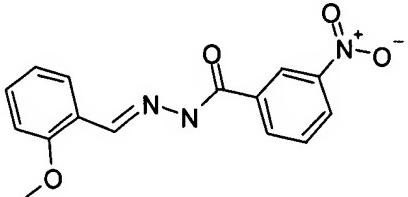
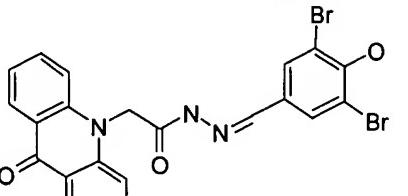
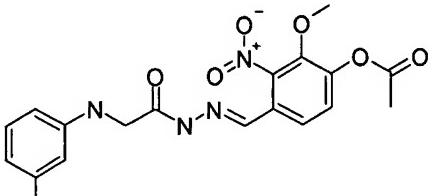
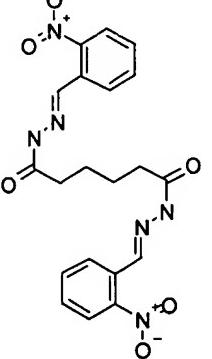
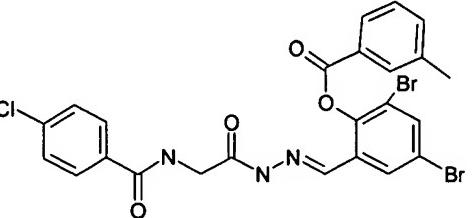
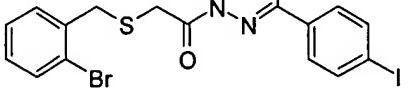
D9.012		416.9*
D9.013		431.9*
D9.014		456.1*
D9.015		465.4*

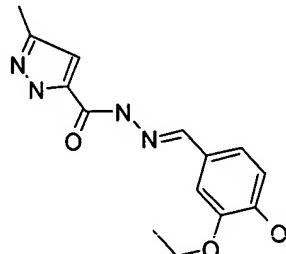
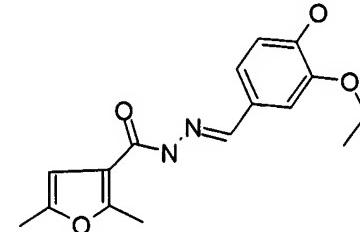
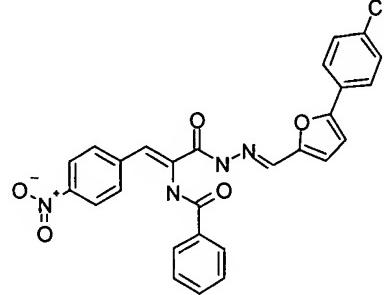
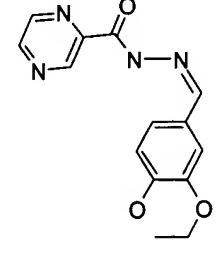
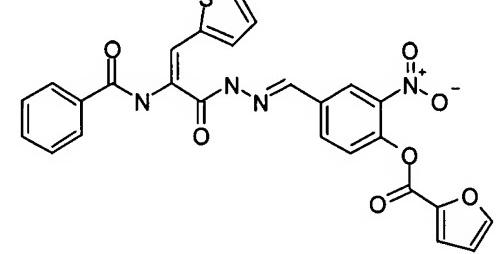
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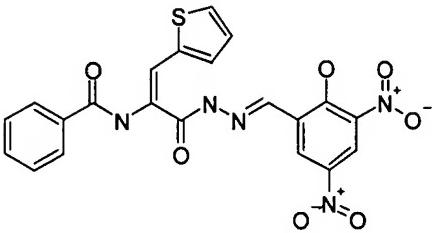
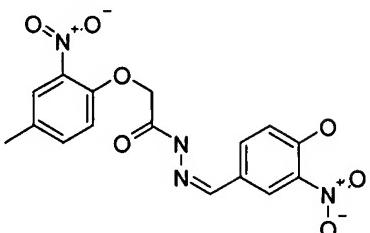
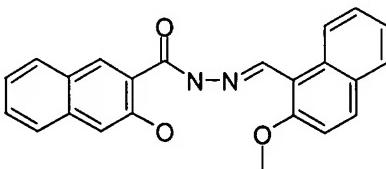
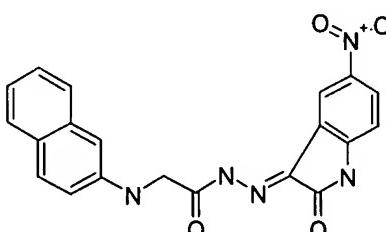
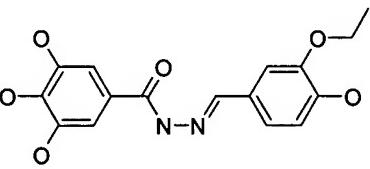
Compound ID.	Structure	IC50_{DPIV} [μM]
D10.001		1.0*
D10.002		2.0*
D10.003		2.9*
D10.004		6.5

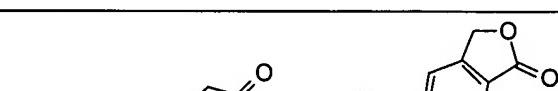
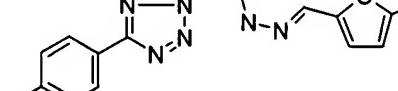
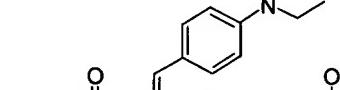
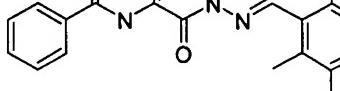
D10.005		6.6
D10.007		7.2*
D10.008		7.6
D10.009		8.1
D10.010		9.1

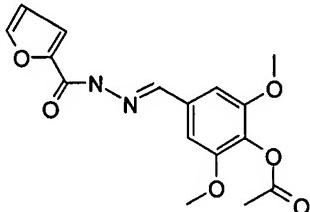
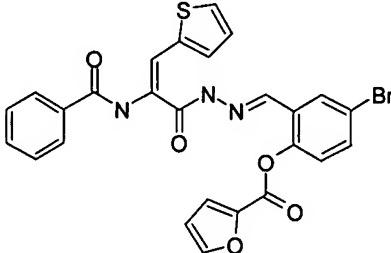
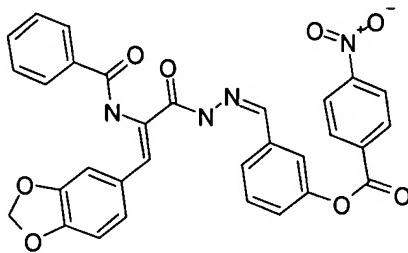
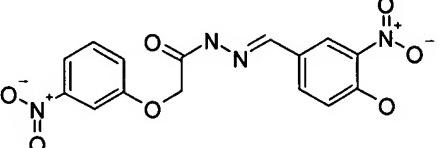
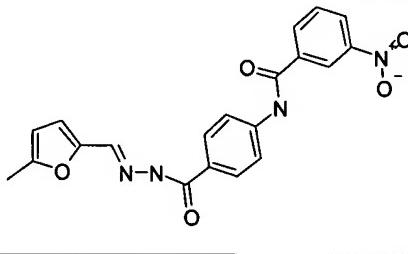
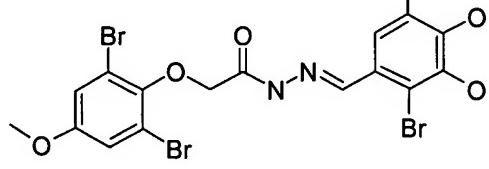
D10.011		9.9
D10.012		10.0
D10.013		10.2
D10.014		11.4
D10.015		12.2
D10.016		12.3

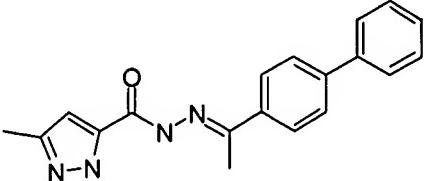
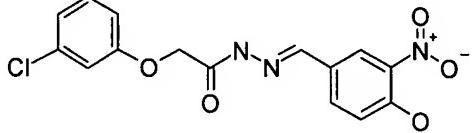
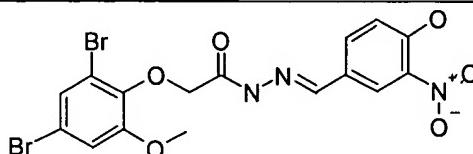
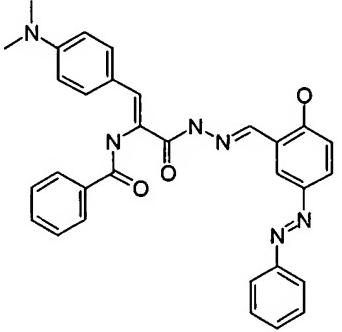
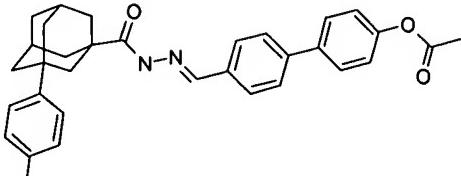
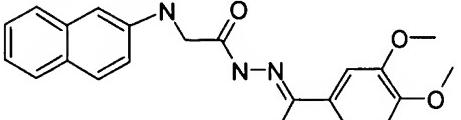
D10.017		12.3
D10.018		12.4
D10.019		12.7
D10.020		12.8
D10.021		13.2
D10.022		13.2

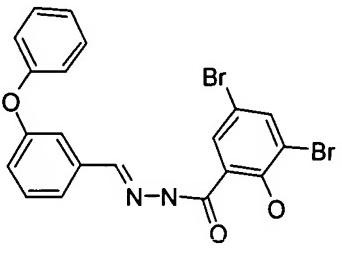
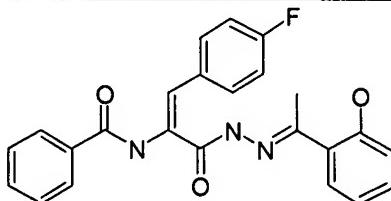
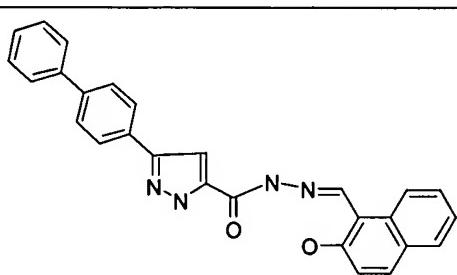
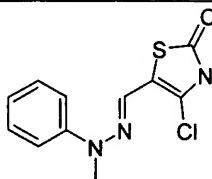
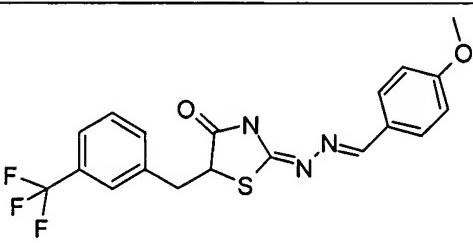
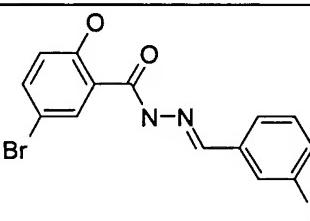
D10.023		13.6
D10.025		16.2
D10.026		16.4
D10.027		16.7
D10.028		16.7

D10.029		17.5
D10.030		17.8
D10.031		17.8
D10.032		18.2
D10.033		18.9
D10.034		19.1

D10.035		20.0
D10.036		20.3
D10.037		20.4
D10.038		20.5
D10.039		20.8
D10.040		20.9

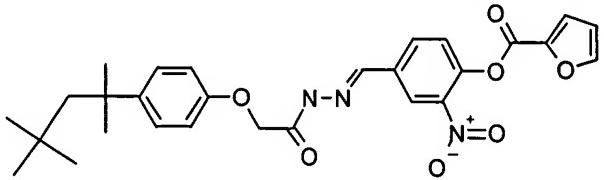
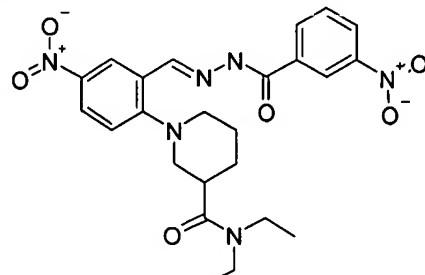
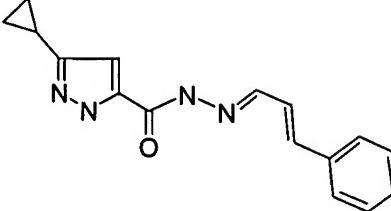
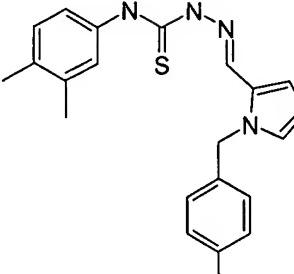
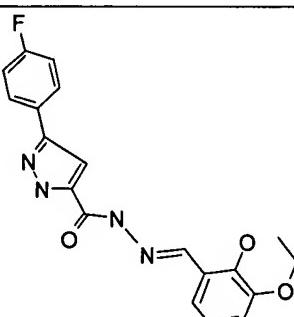
D10.041		21.8
D10.042		24.1
D10.043		24.2
D10.044		24.4
D10.045		28.8
D10.046		29.2

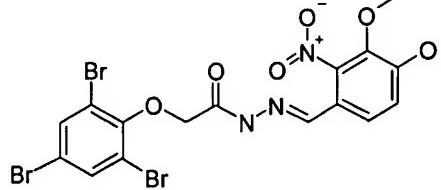
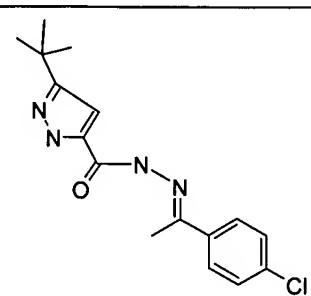
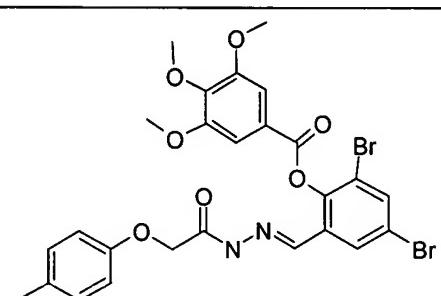
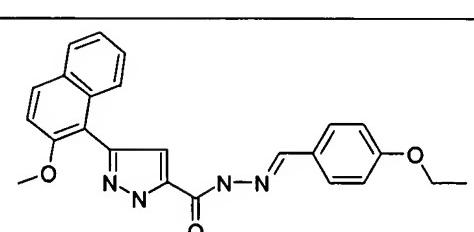
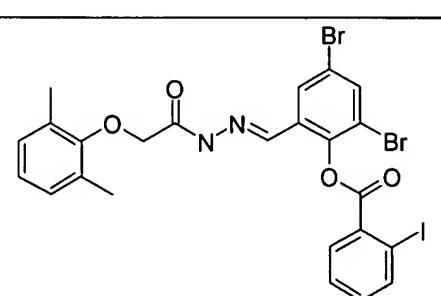
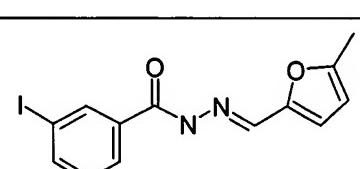
D10.047		29.8
D10.049		31.9
D10.050		32.1
D10.051		33.9
D10.052		32.9
D10.053		32.9

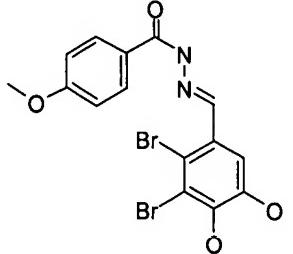
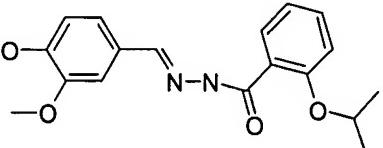
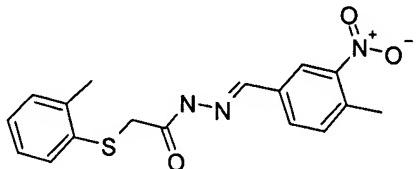
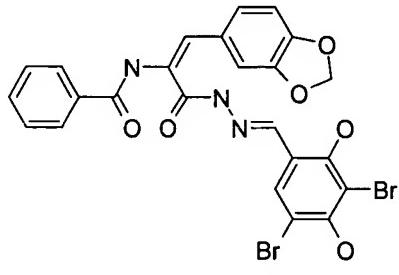
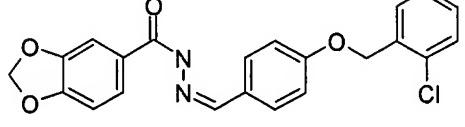
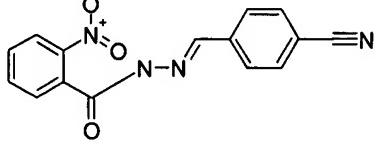
D10.054		33.3
D10.055		33.4
D10.056		33.5
D10.057		32.4
D10.058		34.2
D10.060		36.3

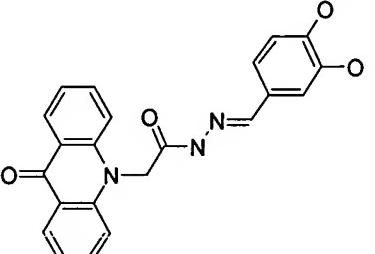
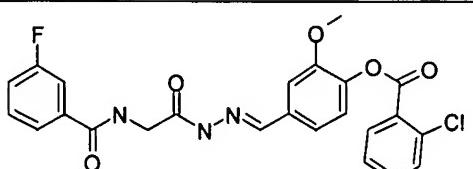
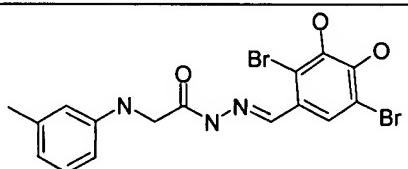
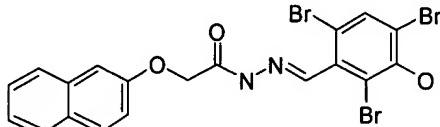
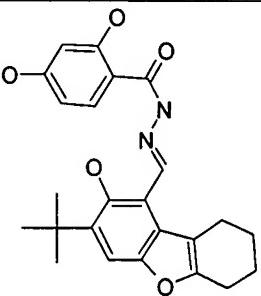
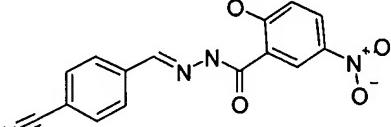
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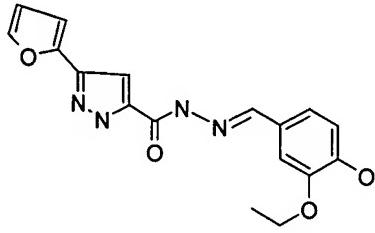
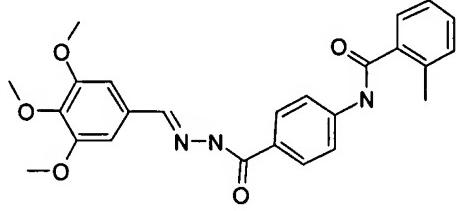
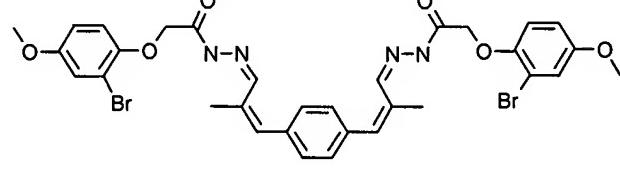
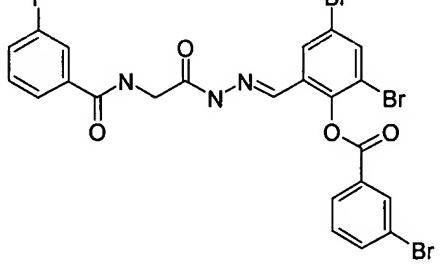
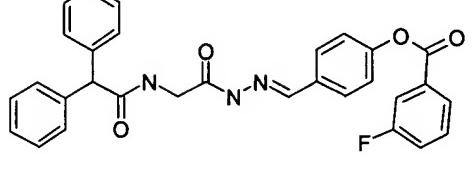
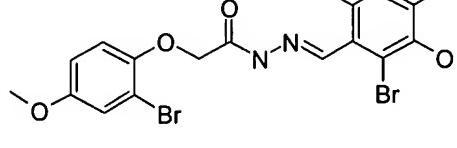
D10.061		39.2
D10.062		39.7
D10.063		40.4
D10.065		41.0
D10.066		42.0
D10.067		45.0

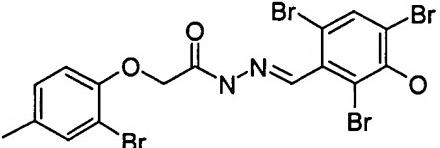
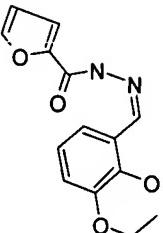
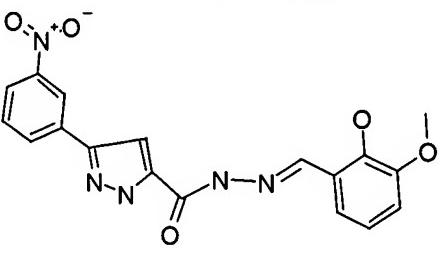
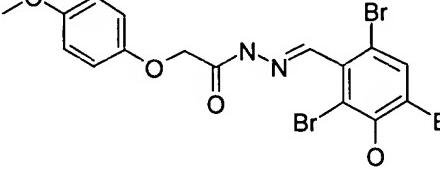
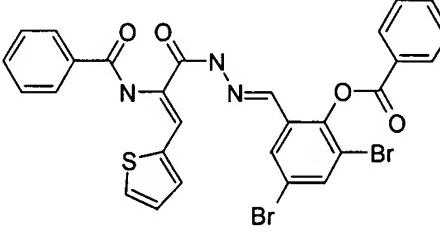
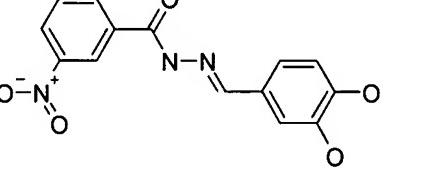
D10.074		52.9
D10.075		54.0
D10.076		55.0
D10.077		55.2
D10.078		55.3

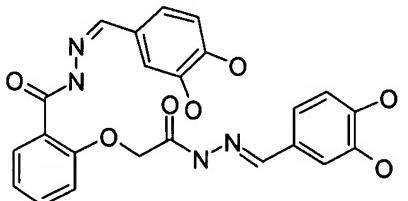
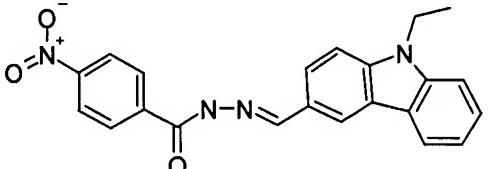
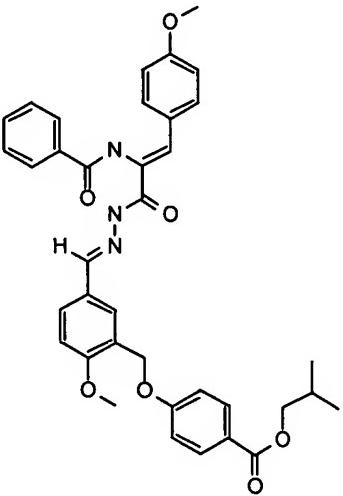
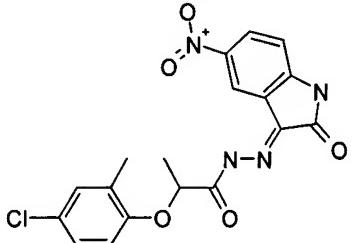
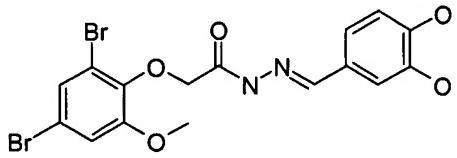
D10.079		55.4
D10.081		55.7
D10.082		55.9
D10.083		56.3
D10.084		57.0
D10.085		57.7

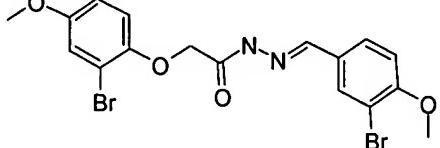
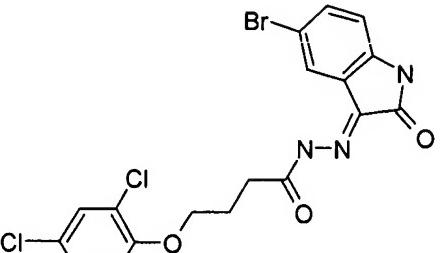
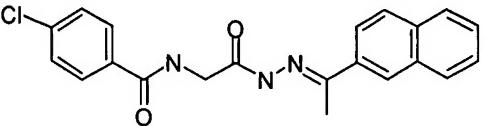
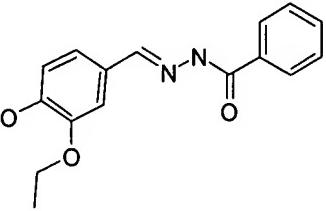
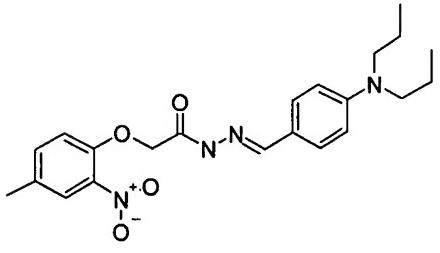
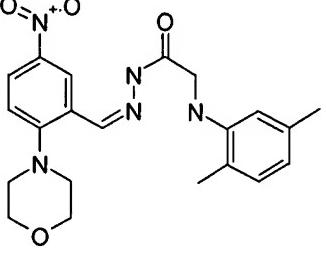
D10.086		57.8
D10.087		58.7
D10.088		58.8
D10.089		60.0
D10.090		62.1
D10.091		62.2

D10.092		63.5*
D10.093		63.5
D10.094		65.5*
D10.095		69.6
D10.097		74.7*
D10.098		81.4

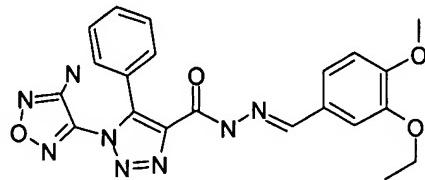
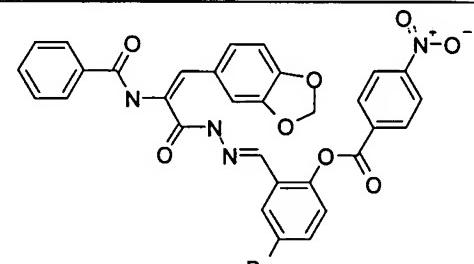
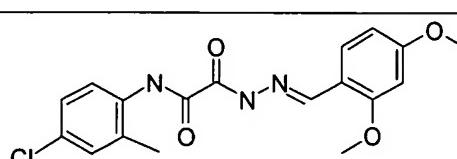
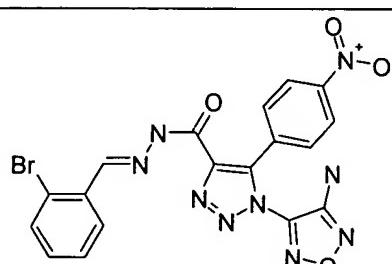
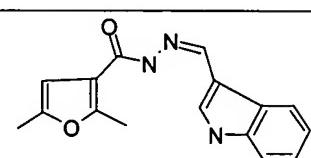
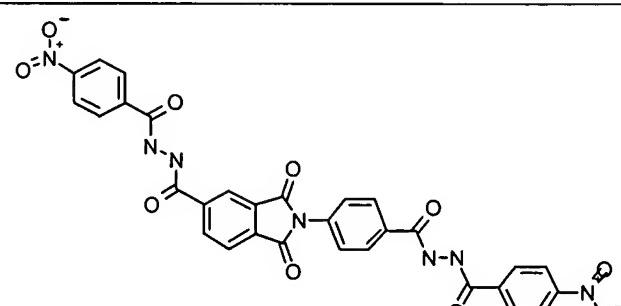
D10.099		84.9
D10.100		91.0*
D10.101		91.3
D10.102		91.9*
D10.103		93.3
D10.105		99.4

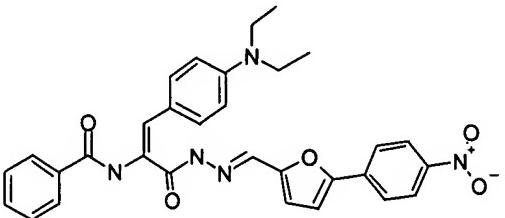
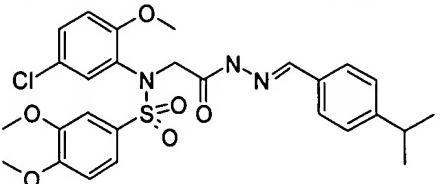
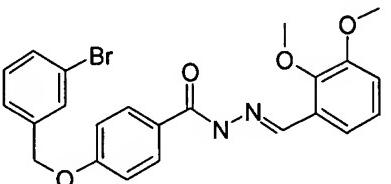
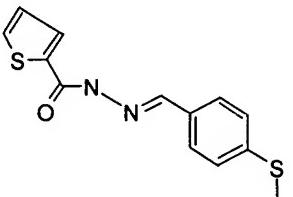
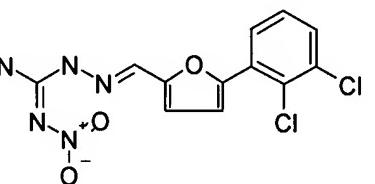
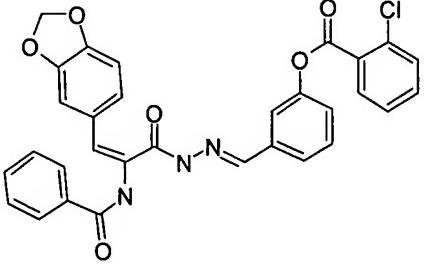
D10.106		101.4*
D10.107		102.6*
D10.108		110.0
D10.109		113.1
D10.110		113.8*
D10.111		115.9*

D10.113		126.8*
D10.116		165.3*
D10.117		165.9*
D10.118		165.9*
D10.119		177.0*

D10.120		197.2*
D10.121		203.8*
D10.122		208.3*
D10.123		217.7*
D10.124		224.8*
D10.125		232.7*

D10.126		233.6*
D10.128		241.4*
D10.129		243.2*
D10.130		255.3*
D10.131		257.4*

D10.132		271.4*
D10.133		271.8*
D10.134		275.1*
D10.135		314.0*
D10.136		339.7*
D10.137		401.9*

D10.138		417.9*
D10.139		431.9*
D10.140		457.7*
D10.141		498.0*
D10.142		609.2*
D10.143		655.7*

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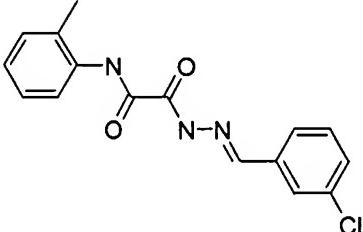
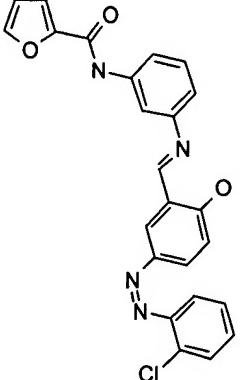
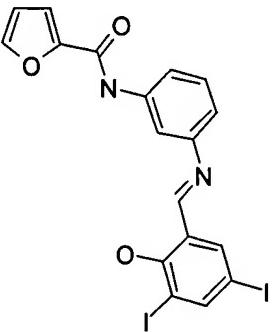
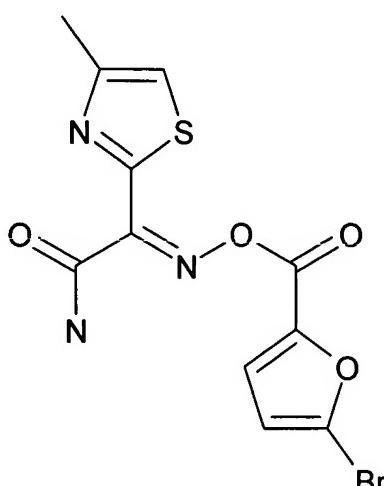
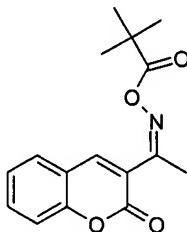
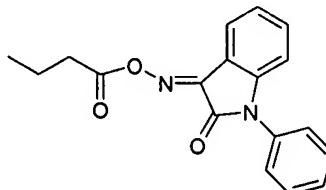
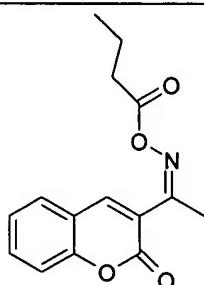
D10.144		775.2*
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Table 11:

Compound ID.	Structure	IC50 _{DPIV} [μM]
D11.001		2.5*
D11.002		9.2

D11.003	 The structure shows a 2-thienyl group attached to a central carbon atom. This carbon is also bonded to a 5-methyl-2-thienyl group at the 2-position, an acetamide group (-CONHCOCH ₃) at the 3-position, and a 2-bromo-4-furyl group at the 4-position.	14.0
D11.004	 The structure shows a chromene core (4H-chromen-3-one) substituted with a 2-acetyl group and a 2-(dimethylamino)acetyl group (-CONH(CH ₃) ₂).	14.1
D11.006	 The structure shows a chromene core (4H-chromen-3-one) substituted with a 2-acetyl group and a 2-(2-methylpropyl)acetyl group (-CONHCH ₂ CH(CH ₃) ₂).	15.2
D11.007	 The structure shows a chromene core (4H-chromen-3-one) substituted with a 2-acetyl group and a 2-propionylacetyl group (-CONHCH ₂ CH ₂ COCH ₃).	18.9

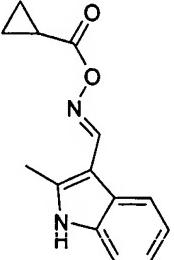
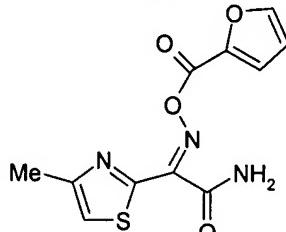
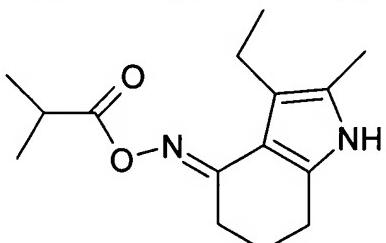
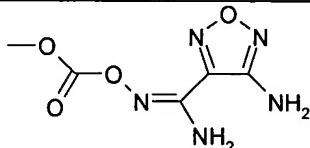
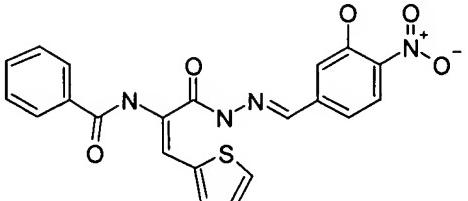
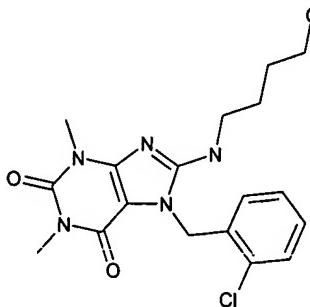
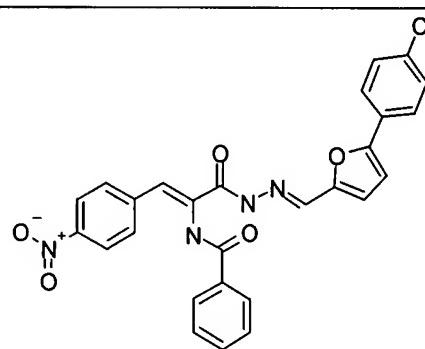
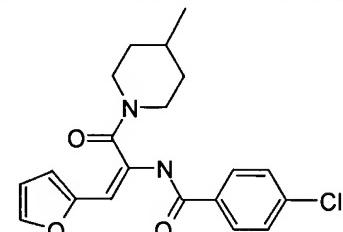
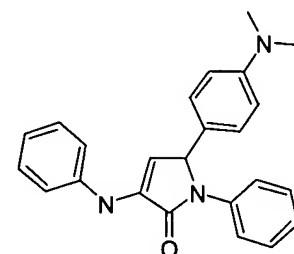
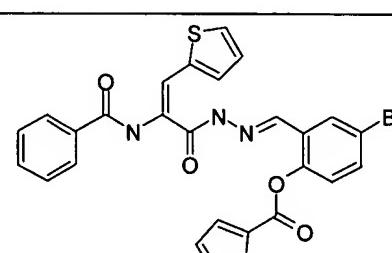
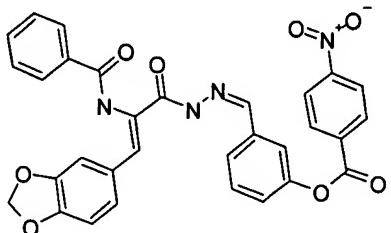
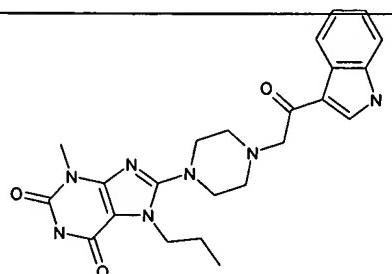
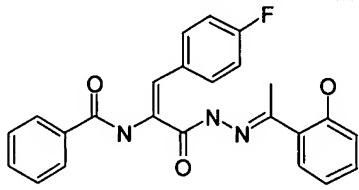
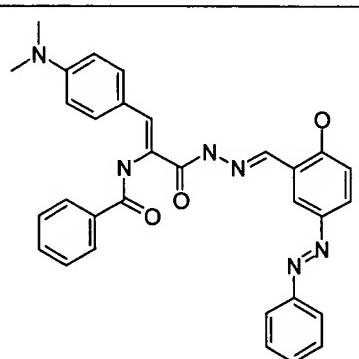
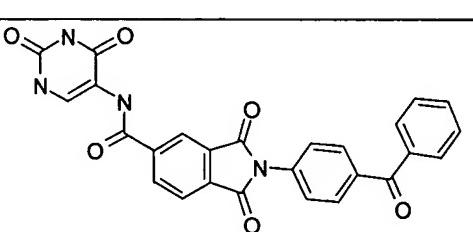
D11.008		30.0
D11.009		32.8
D11.010		43.8
D11.011		44.3

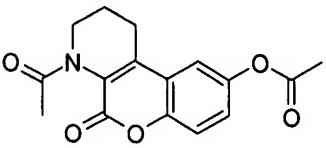
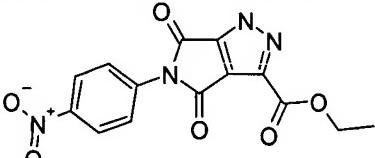
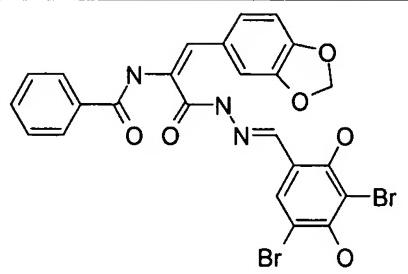
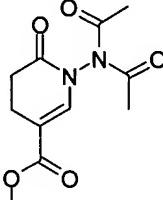
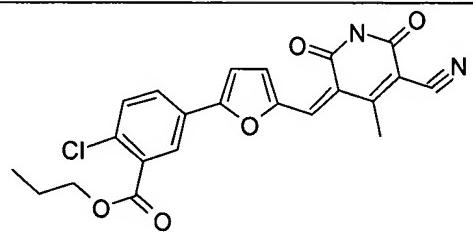
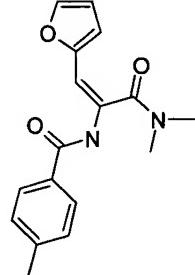
Table 12:

Compound ID.	Structure	IC50 _{DPIV} [μM]
D12.001		6.5

D12.002		16.2
D12.003		16.4
D12.004		18.5
D12.006		20.4
D12.009		24.1

D12.010		24.2
D12.012		30.8
D12.013		33.4
D12.014		33.9
D12.016		38.2

D12.017		34.2
D12.019		39.2
D12.024		46.2
D12.025		46.5
D12.027		49.0

D12.029		59.4
D12.031		54.5
D12.032		60.0
D12.033		60.7
D12.034		65.3
D12.038		47.7

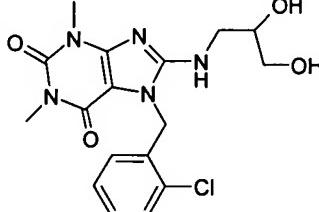
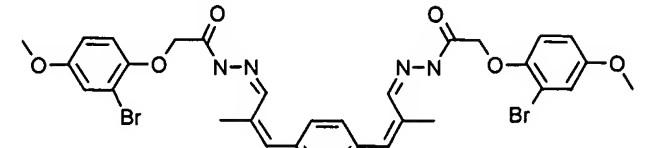
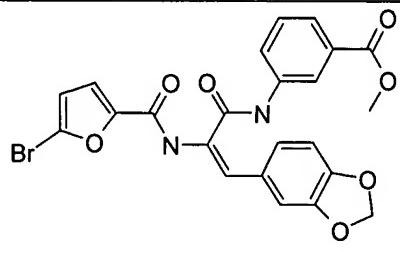
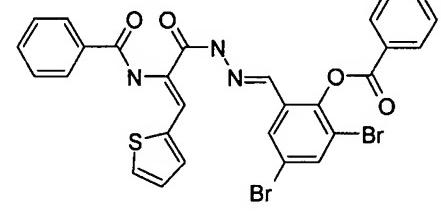
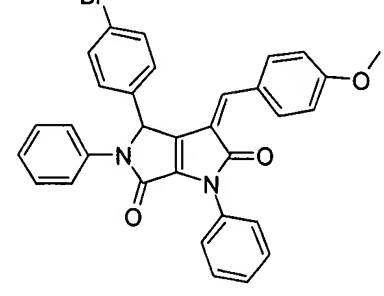
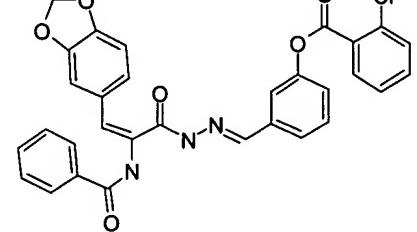
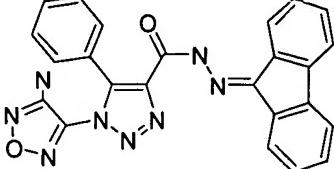
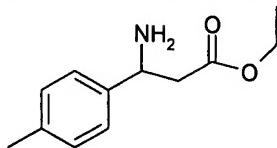
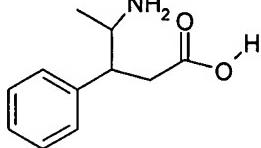
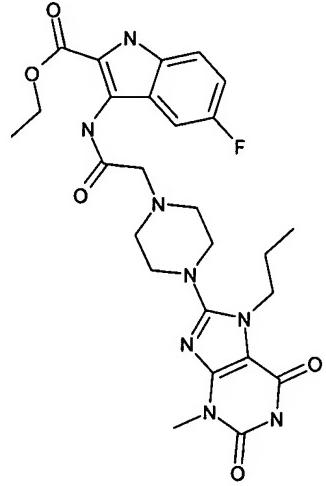
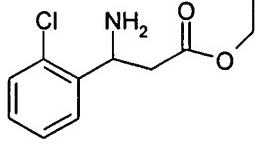
D12.040		83.3*
D12.042		91.3
D12.043		92.2*
D12.045		113.8*
D12.047		198.3*
D12.050		655.7*

Table 13:

Compound ID.	Structure	IC50_{DPIV} [μM]
D13.001		10.1
D13.002		23.3
D13.003		38.0
D13.004		69.8*
D13.005		72.2

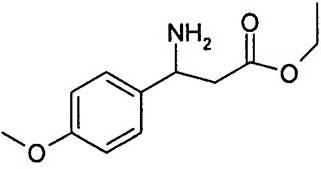
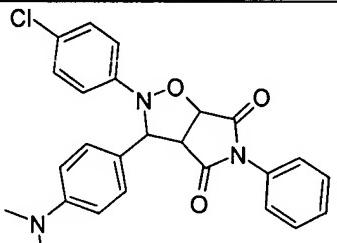
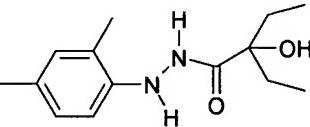
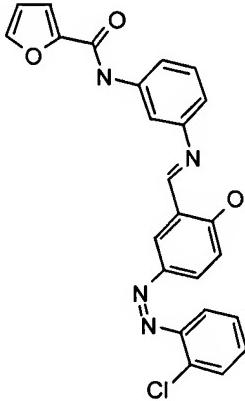
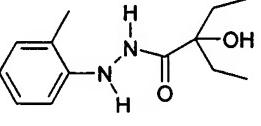
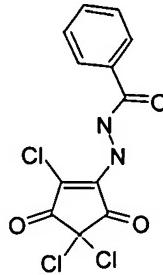
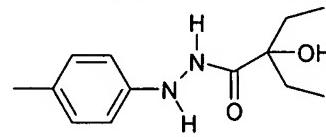
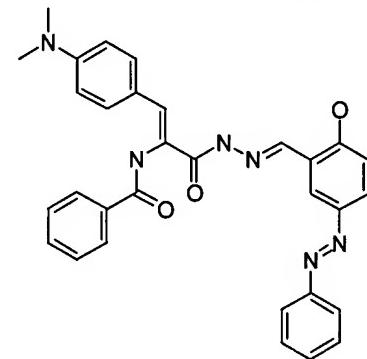
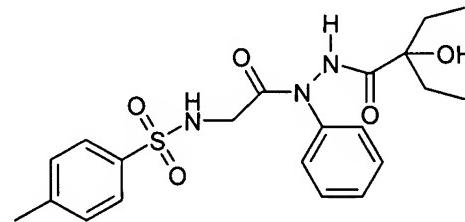
D13.006		83.3*
D13.007		343.7*

Table 14:

Compound ID.	Structure	IC50 _{DPIV} [μM]
D14.001		1.2*
D14.002		2.5*
D14.003		5.7

D14.004		26.2
D14.005		26.7
D14.006		33.9
D14.007		456.1*

Example 2:

Therapeutic effect of the combined inhibition of the dipeptidyl peptidase IV and of enzymes having an analogous effect as well as of the alanyl aminopeptidases and of enzymes having an analogous effect on the experimental autoimmune encephalomyelitis (EAE) of mice (animal model of multiple sclerosis)

The disease EAE was induced by a daily injection of PLP139-151 (myelin antigen proteolipide protein peptide 139-151) to SJL/J mice ($n = 10$). After the outbreak of the disease, there was, on the 11th day after the immunization, a therapeutic intervention by an intraperitoneal injection of 1 mg of each of the peptidase inhibitors on the first day and further injections of 0.5 mg of each of the inhibitors on each second day. The disease scores [vD1] are defined by differently distinct degrees of paralysis. Healthy animals have the disease score 0. Actinonine was used as the alanyl aminopeptidase inhibitor, Lys[Z(NO₂)] pyrrolidide was used as the dipeptidyl peptidase IV inhibitor. The treatment was effected for the time of 46 days after the immunization. The results are shown in Figure 1. The course of the curves demonstrate unequivocally a particularly strong and long-lasting [vD2] therapeutic effect after a combined inhibition of both peptidases.

Example 3:

Therapeutic effect of the combined inhibition of the dipeptidyl peptidase IV and of enzymes having an analogous effect as well as of the alanyl aminopeptidases and of enzymes having an analogous effect on the dextran sulfate-induced colitis of mice (animal model of chronical inflammatory intestinal diseases)

An inflammation relating predominantly to the colon (equivalent to the disease of human Colitis ulcerosa) was induced by an administration of 3 % sodium dextran sulfate dissolved in the drinking water of female Balb/c mice having an age of 8 weeks. After three days, all animals showed clear symptoms typical for the disease. The peptidase inhibitors (or phosphate-buffered saline as a placebo) were administered intraperitoneally from day 5 on three successive days. The degree of the disease is determined in accordance with an acknowledged evaluation system (score). The following parameters are considered when determining the score: Consistency of the excrements (solid = 0 points (pts.); pasty = 2 pts.; liquid/like di-

arrhea = 4 pts.); detection of blood in the excrements (no blood = 0 pts.; occult blood = 2 pts.; evident = 4 pts.); loss of weight (0 – 5 % = 0 pts.; 5 to 10 % = 1 pts.; 10 – 15 % = 2 pts.; 15 – 20 % = 3 pts.; > 20 % = 4 pts.). Healthy animals have a score value of 0 pts.; the maximum value are 12 pts.. From 10 pts. on, the disease is lethal. In the course of the disease, the score value increases due to the change of the excrement parameters. Later-on (starting from day 5), the loss of weight increases the score. Figure 2 shows the disease intensity for untreated and treated animals on the day 7 after three days of therapy.

The application of 10 µg of the respective single prior art inhibitors ($n = 14$ per group; see explanation) achieved a slight, but insignificant reduction of the heaviness of the disease (- 16.5 % by a treatment with actinonine; - 12.3 % by a treatment with Lys[Z(NO₂)] pyrrolidide). An i.p. application of a combination of the two peptidase inhibitors resulted into a statistically significant ($p = 0.00189$) improvement of the disease by 40 %.

Example 4:

Therapeutic effect of the combined inhibition of dipeptidyl peptidase IV and of enzymes having an analogous effect as well as of the alanyl aminopeptidase and of enzymes having an analogous effect on the ovalbumine-induced asthma bronchiale of mice (animal model of human asthma bronchiale). Figure 3 shows the influence of the combined peptidase inhibition on the reduction of the average expiratory flux (EF 50) as a measure of the pulmonary function (Figure 3 A) as well as on the eosinophilia as a characteristic feature of the asthma bronchiale pulmonal inflammation (Figure 3 B).

Female Balb/c mice were sensitized for the antigen ovalbumine capable of inducing asthma bronchiale by an intreperitoneal administration of 10 µg ovalbumine on the days 0, 14 and 21. On day 27/28, the animals received a boosting dose of

ovalbumine by inhalation [vD3]. After an intreperitoneal administration of the peptidase inhibitors on the days 28 – 35, there was effected an intranasal ovalbumine challenge on day 35, as well as a check of the allergic premature reaction via the pulmonal function. There were measured: the average expiratory flux (EF50), the tidal volume, the respiration rate and the minute volume as well as the number of eosinophilic granulocytes in the bronchoalveolar lavage. 8 to 10 animals were used per experimental group. By way of example, in Figure 3 A, there is summarized the effect of the peptidase inhibitors on the reduction of the EF50 value. The alanyl aminopeptidase inhibitor actinonine (group B; 0.1 mg), and the dipeptidyl peptidase IV inhibitor Lys[Z(NO₂)] pyrrolidine as well (group C; 0.1 mg), showed a therapeutic effect. Significant therapeutic effects, however, were obtained only when using combinations of both inhibitors (group D; 0.1 mg of each of the inhibitors). Group E represents animals which were not sensitized by OVA, but which were subjected – beyond that – all procedures to which the animal groups A to D were subjected. Hence, this group is a group of healthy, non-allergic animals allowing to calculate stress-induced effects on the pulmonal function.